A Pilot Study of Local Anesthesia for Inguinal Hernia Surgery in Older Adults

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PREFACE

The Clinical Intervention Study Protocol Template is a suggested format for clinical trials sponsored by the National Institute on Aging (NIA). Investigators are encouraged to use this format, as appropriate, when developing protocols for their studies. Large multi-site observational studies will also benefit from this protocol template.

Note that instructions and explanatory text are indicated by italics and should be replaced in your protocol with appropriate text. Section headings and template text formatted in regular type should be included in your protocol document as provided in the template.

The goal of this template is to provide a general format applicable to all single- and multicenter clinical intervention trials (e.g., drug, surgery, behavioral, nutritional, device, etc).

As you can see the version number and date are on the bottom of each page. When making changes to an approved and "final" protocol, please provide a summary of the changes, with the date, at the front of the protocol.

A PILOT STUDY OF LOCAL ANESTHESIA FOR INGUINAL HERNIA SURGERY IN OLDER ADULTS

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Supported by:

The National Institute on Aging

(Include application or grant number(s) when available)

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PRÉCIS

A Pilot Study of Local Anesthesia for Inguinal Hernia Surgery in Older Adults

Objectives

The primary objective is to conduct a pilot randomized trial comparing outcomes of inguinal hernia surgery under local versus general anesthesia to (1) demonstrate our ability to successfully recruit, randomize, and retain patients aged 65 years and older for a randomized trial of local versus general anesthesia for inguinal hernia surgery, and (2) establish our ability to measure relevant outcomes and test protocols and study instruments for measuring key outcomes. The secondary objective is to generate preliminary comparisons between the two study arms, to inform design of a larger multisite trial.

Design and Outcomes

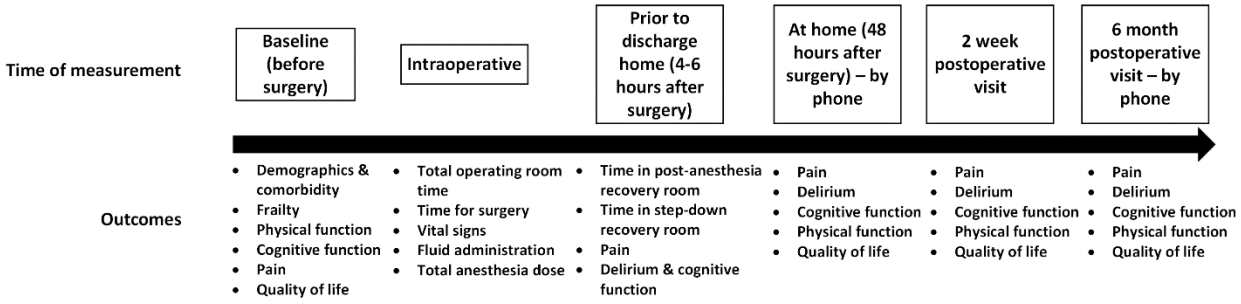

Figure 1. Measurement of baseline status & endpoints for pilot trial. We will collect baseline characteristics prior to surgery. Intraoperative and immediate postoperative outcomes include time, pain, and cognitive recovery. Post-discharge outcomes include pain, cognitive & physical function, and quality of life.

This is a single-blind randomized pilot trial of intraoperative and postoperative outcomes for patients aged 65 years and older who have inguinal hernia repair under either local or general anesthesia. Study coordinators will be blinded to whether patients are randomized to local or general anesthesia and we will assess the outcomes shown in Figure 1. The investigative team (except for statistician) will be blinded to treatment assignment until the final analysis is complete.

Interventions and Duration

The interventions being compared are (1) local anesthesia versus (2) general anesthesia for inguinal hernia surgery. As shown in Figure 1, patients will be on study for six months after surgery (total follow-up period of six months).

Sample Size and Population

We will enroll participants from two sites: Houston and Dallas. We will seek to enroll 40 patients in each of the two study arms (local and general anesthesia) for a total of 80 patients. We will not stratify based on (1) hospital site, and (2) age (65-75 years and 75+ years of age). We will include all patients aged 65 years and older who are having elective open inguinal hernia surgery for a unilateral and non-incarcerated hernia. We will exclude patients with prior hernia repair on the same side, contraindications to

general anesthesia, allergies to local anesthesia, incarceration or bowel strangulation, or evidence of an active infection.

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1 STUDY OBJECTIVES

1.1 Primary Objective

To conduct a pilot randomized trial comparing outcomes of inguinal hernia surgery under local versus general anesthesia for adults aged 65 years and older. This will establish feasibility of conducting a multisite randomized trial and will optimize study procedures prior to conducting the multisite trial. We will measure

(1) Rates of enrollment, percent of eligible patients enrolled, and reasons for non-enrollment
(2) Proportion of participants completing all study visits
(3) Proportion of missing data
(4) Time to complete study evaluations and instruments
(5) Participant satisfaction with study procedures and instruments
(6) Whether survey instruments can be eliminated due to redundancy
(7) Estimated sample size for a fully powered trial

We hypothesize that:
(1) Based on our preliminary data, at least 75% of eligible patients will agree to be randomized.
(2) We will be able to follow 100% of patients up to their 2 week postoperative visit (as essentially all patients keep this appointment in our clinical practice), and that we will be able to follow at least 90% of patients at the six month time point.
(3) Missing data on study instruments will be <5%
(4) Overall time burden for instrument completion will be acceptable to patients
(5) One or more study instruments can be eliminated (thus reducing the time burden) because the other instruments may predict a substantial portion of variance
(6) We will be able to use data from the pilot to estimate the necessary sample size for a multisite randomized trial

1.2 Secondary Objectives

Generate preliminary comparisons between the two study arms, to inform design of a larger multisite trial. Clinical outcomes that will be measured include:

(1) Quality of life
(2) Physical function
(3) Cognitive function
(4) Pain
(5) Postoperative complications
(6) Operative and anesthesia times
(7) Recovery time (time spent in the post-anesthesia care and stepdown units)

We hypothesize that there will be sufficient data to estimate effect size (based on

means/medians and dispersion) for these key outcomes.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Inguinal hernia repair - the most common general surgery operation in the U.S. - provides a unique opportunity to improve outcomes for older patients by changing surgical practice.[1] Nearly 80% of inguinal hernia operations are performed under general anesthesia versus 15%-20% using local anesthesia, despite the absence of evidence for superiority. [2,3] The choice of anesthesia has particular implications for older adults because they face substantial short- and long-term risk of cognitive and physical decline after exposure to general anesthesia. [4,5] Consequently, the American College of Surgeons and the American Geriatrics Society have identified a critical need in surgery: determining which operations have better outcomes when performed under local rather than general anesthesia.[4]

Currently, the evidence for choosing an anesthesia technique for inguinal hernia repair in older adults is inconclusive. Several small randomized trials and cohort studies have suggested that using local anesthesia for hernia repair reduces morbidity by one-third, unplanned admissions by 20%, and operative time and costs by 15%, while other studies showed no significant differences. [2,6-8] However, there are significant flaws in these studies that severely limit their applicability to older adults: (1) They mainly focused on younger patients with limited comorbidity burden, largely ignoring individuals aged 65 years and older, (2) They did not adequately examine the effects of general anesthesia on cognitive function and quality of life for older adults and their caregivers. In particular, the only randomized trial that evaluated neurocognitive recovery evaluated a mostly younger population and did not look specifically at outcomes for older adults where the largest benefit is expected to occur.[8] (3) They did not consult with stakeholders (patients, caregivers, physicians, hospitals, or health systems) to identify outcomes relevant to those groups. There is an urgent need to evaluate benefits of local anesthesia for inguinal hernia repair in older adults because the proportion of Americans age 65 and older is rapidly growing and will reach 20% of the population in the next 10 years. [9] Improving postoperative recovery for patients having the most common general surgery operation in our country will have a tremendous effect on patient and caregiver quality of life.

2.2 Study Rationale

The study rationale is that prior to conducting a multisite randomized trial, it is necessary to identify relevant outcomes, understand barriers to greater use of local anesthesia, test study procedures, and confirm our ability to adequately recruit and randomly assign participants. Additionally, the proposed study will provide the applicant with critical training in the design, conduct, and analysis of clinical trials. This will uniquely position the applicant to change surgical care for older adults.

There have been two prior randomized clinical trials that compared local versus general anesthesia for inguinal hernia repair. Nordin et al. randomized 616 patients in Sweden to local,

regional, or general anesthesia.[10] They did not specifically look at older patients but the mean age in each group was 56 years old. They found that the total operative time was five minutes faster for the local anesthesia group (90 versus 95 minutes) the incidence of postoperative pain requiring opioids and catheterization for urinary retention was decreased by 29% for the local compared to general anesthesia group and the rate of unplanned admission was decreased by 19%. A cost-effectiveness analysis conducted by the same group indicated that hospital costs were lower in the local anesthesia group (a difference of €311/$378) and total healthcare costs were also lower (€316/$384). A second trial from Scotland randomized 279 patients to local or general anesthesia, with a mean age of 55 years for both groups.[8] This study did not find a significant difference in operative time, complications, length of stay, pain, or neurocognitive recovery as measured by a battery of tests. However, like the paper by Nordin et al., they did not specifically analyze outcomes in older patients which would tend to dilute the potential benefits of local anesthesia. Equally important, this study focused almost exclusively on healthy patients with smaller hernias, as evidenced by >90% of patients having an American Society of Anesthesiology score of 1 or 2 and a mean total surgical time of 48 minutes for each group (nearly 50% of operative time in the Nordin study).

There are several observational studies that compare outcomes from hernia repair under local or general anesthesia, and these mostly suggest that local anesthesia is associated with shorter operative time (5-10 minutes), fewer complications (1-3% reduction), and enhanced quality of life. [2,11-15] However, only two of these studies look specifically at outcomes for older adults and both suffer from a poor approach to risk adjustment.[11,12] Additionally, all the observational studies have a limited assessment of complications and failed to effectively evaluate rates of urinary retention and catheterization after surgery. Urinary retention is the most common complication of general anesthesia after hernia repair and results in considerable discomfort for patients who are catheterized to relieve it. Additionally, when patients do not resolve retention in a timely fashion, it results in the need for unplanned admission which increases hospital costs.[6]

The intervention chosen for testing in this study is the choice of anesthesia (local or general) for unilateral inguinal hernia repair. These are the primary methods of anesthesia for inguinal hernia surgery by most surgeons (though some perform the operation under spinal or regional anesthesia, this is rare). Both approaches are used in clinical practice with acceptable known risks and complications. General anesthesia is associated with risks of hypotension, venous thromboembolism, heart attack, stroke, pulmonary dysfunction, cognitive dysfunction, allergic reaction, and malignant hyperthermia. The main risks of local anesthesia include allergic reaction and hypotension (when the anesthetic is improperly injected into a blood vessel).

3 STUDY DESIGN

3.1 Summary & objectives

This will be a pilot randomized trial with two arms for patients having open unilateral inguinal hernia repair: (arm 1) local anesthesia versus (arm 2) general anesthesia. Each arm will recruit 40 patients.

The primary objective is to conduct a pilot randomized trial comparing outcomes of inguinal

hernia surgery under local versus general anesthesia for adults aged 65 years and older. This will demonstrate feasibility of conducting a multisite randomized trial and will optimize study procedures prior to conducting the multisite trial. The secondary objective is to generate preliminary comparisons between the two study arms, to inform design of a larger multisite trial.

The study design is illustrated in Figure 1.

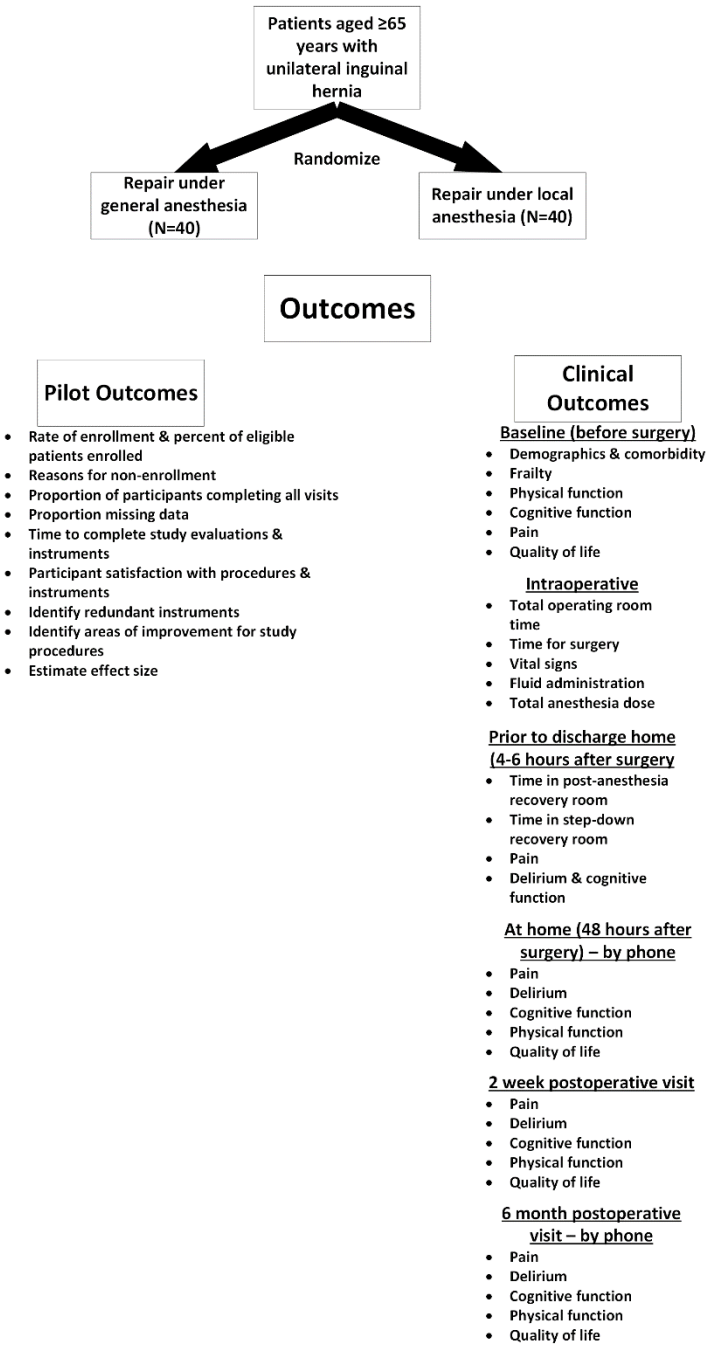

Figure 1. Overview of study design. Patients will be randomized to inguinal hernia surgery under either local or general anesthesia. We will collect baseline characteristics prior to surgery. Intraoperative and immediate postoperative outcomes include time, pain, and cognitive recovery. Post-discharge outcomes include pain, cognitive & physical function, and quality of life. All outcomes collected in-person unless otherwise noted

3.2 Study population

The target population is patients aged 65 years and older who are having elective, open inguinal hernia surgery for initial, non-incarcerated, unilateral inguinal hernias.

3.3 Study location

The study will be conducted at general surgery clinics for 2 sites:

(1) VA North Texas Healthcare System in Dallas, TX
(2) Michael E DeBakey VA in Houston, TX

3.4 Duration of enrollment and follow up

Participants will be followed for a total of 6 months after surgery. For total study duration, recruitment will start 18 months after funding begins and will conclude after a total of 24 months of recruitment. Data collection will terminate 6 months after the last patient is enrolled.

3.5 Randomization and stratification

We will randomly assign older patients having inguinal hernia surgery to one of the two study arms: (1) local anesthesia or (2) general anesthesia. Our goal for enrollment will be 40 patients in

each arm, equally distributed by site. We will use a stratified randomization scheme with blocking within strata. Stratification factors include hospital location (Dallas or Houston) and age (65-75 or 75+ years). Equal allocation by strata will be used so that differences among hospitals and age groups will be balanced.

3.6 Blinding

Research assistants will be blinded to study assignment when conducting all assessments.

A description of the trial design should include:

- *Type/design of trial (e.g., placebo-controlled, double-mask, parallel design, open-label, dose escalation, dose-ranging)*
- *Specific statement of the primary and secondary outcomes (must be consistent with Study Objectives)*
- *Study population and groups/arms including sample size (including a table, if appropriate)*
- *Study location (e.g., in-patient or out-patient, clinic, community)*
- *Approximate duration of enrollment period and follow-up (specify individual participant vs. entire trial)*
- *Description of intervention and administration*
- *Randomization, blinding and any stratification*
- *Other protocol specific details, such as centralization of evaluations (e.g., central laboratory or central reading center for clinical scans)*

3.7 Study timeline

Table 1 (next page) outlines the study timeline. This includes completion of proposal aims 1 and 2, which will identify and prioritize study outcomes to supplement the list of measurements shown in section 6. Pre-trial data collection and analysis of interviews and focus groups will be completed by 18 months. We will then begin recruiting participants for the pilot randomized trial over a period of 24 months, allowing an additional 6 months for follow up of the last enrolled participant. In year 3, we anticipate beginning to write manuscripts and our R01 application based on the data from our pilot study. This will leave sufficient time to revise the grant in year 4 if the initial submission is not funded.

Table 1. Study timeline, including pre-trial activities (aims 1 and 2)

	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48
Aims 1 and 2 (Pre-trial)								
Interviews to identify patient outcomes								
• Conduct interviews	X	X	X					
• Analyze data	X	X	X					
Focus groups to identify surgeon, anesthesia, & leadership outcomes								
• Conduct focus groups		X	X					
• Analyze data		X	X					
Prepare and publish manuscripts on qualitative data				X	X			
Aim 3 (Pilot trial)								
Recruit participants			X	X	X	X		
Complete follow up				X	X	X	X	
Analyze pilot outcomes			X	X	X	X	X	
Analyze clinical (secondary) outcomes							X	
Prepare and publish manuscripts on pilot data						X	X	X
Prepare, submit, and revise R01					X	X	X	X

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

Key components of the success of a clinical study are the selection and enrollment of participants who are reasonably representative of the populations or characteristics under investigation to allow for sufficient generalizabilty. This section should define and describe the study population.

4.1 Inclusion Criteria

We will include patients who meet all of the following criteria:

1. Age ≥ 65 years
2. Presenting to clinic with a unilateral inguinal hernia that is not incarcerated
3. Considered suitable for either general or local anesthesia
4. Willing to complete all study requirements, including follow-up continuing until six months after surgery

Provide a statement that participants must meet all of the inclusion criteria to participate in this study and then list each criterion. List as many criteria as necessary to clearly define your study population.

- *Demographic characteristics (e.g. gender, age) and the health state, presence or absence of a medical condition/disease.*
- *Required laboratory results, diagnostic methods, criteria for classification of current status, as measured within XX days prior to randomization. List specific tests and documentation methods.*

- *Prior therapy, if any. Consider listing specific prior treatments. Consider listing the allowable duration of prior therapy for the specific population to be studied (e.g., treatment-naïve, treatment-experienced or prior-treatment-failed "salvage" participants).*
- *Ability to understand study procedures and to comply with them for the entire length of the study.*
- *If men and women of reproductive capability will be enrolled, indicate whether contraception is necessary and required. If yes, include details of allowable contraception methods for trial.*

4.2 Exclusion Criteria

We will exclude patients who meet any of the following criteria:

1. The hernia that the patient is being evaluated for has undergone prior repair (ipsilateral recurrent hernia)
2. Any contraindications to general anesthesia (including malignant hyperthermia)
3. Allergies to local anesthesia
4. Evidence of hernia incarceration or bowel strangulation
5. Active local or systemic infection that would preclude the use of mesh for hernia repair
6. Need for concurrent surgical procedure at the time of hernia repair
7. English is not the patient's primary language
8. Enrollment in other research studies

Patients with dementia or other cognitive dysfunction will not be excluded as long as there is a caregiver available to participate in the consent and follow-up procedures.

Provide a statement that all candidates meeting any of the exclusion criteria at baseline will be excluded from study participation and then list each criterion.

List as many criteria as necessary to clearly define your study population.

- *Specify health status or any clinical conditions (e.g., life expectancy, co-existing disease) or other characteristics that precludes appropriate diagnosis, treatment or follow-up in the trial.*
- *Clinical/laboratory indicators of current status, obtained within XX days prior to randomization. List the specific tests to be performed and the narrowest acceptable range of laboratory values for exclusion, consistent with disease and/or safety. Include as many as necessary.*
- *Specify any exclusion related to pregnancy, lactation, or plans to become pregnant. Specify methods for assessing current status and willingness to use contraception, if applicable. Include as many as necessary.*

- *Use of [excluded drugs, behavioral interventions, devices, etc.] within XX days prior to study entry. Treatment with another investigational drug or intervention (with time frame).*
- *For drug studies: allergy/sensitivity to study drugs or their ingredients.*
- *Cancer*
- *Current drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.*
- *Inability or unwillingness of individual or legal guardian/representative to give written informed consent.*

4.3 Study Enrollment Procedures

4.3.1 Identification and recruitment

Each day, research assistants will screen the list of clinic appointments over the next 24-48 hours for general surgery clinics at both sites to identify patients referred for evaluation of inguinal hernias. Once potential participants are identified, research assistants will attend the clinic and wait for faculty surgeons to decide whether patients are candidates for inguinal hernia repair. If potential participants are deemed surgical candidates, then the research assistant will go with the faculty surgeon to confirm eligibility and to consent and enroll patients. At the clinic visit, the research assistants will explain the study purpose and procedures, and they will verify eligibility before attempting to recruit and consent patients. Information on all patients screened will be recorded in the study electronic database by the research assistants, who will also note reasons for ineligibility (no surgery scheduled, clinic appointment rescheduled, patient did not come to the clinic appointment, patient is enrolled in another study, etc). Similarly, a notation in the database will be made for all patients who are approached and the reasons for non-participation will be recorded (patient does not want to participate, patient specifically requests one type of anesthesia, patient was missed by the research assistant, etc.).

4.3.2 Consent procedures

The research assistants will bring a written informed consent to the clinic visit and review this with eligible patients. The conversation will include a discussion of the risks and benefits of local and general anesthesia, and a review of the existing evidence supporting the use of each technique in older adults. The consent form will also include discussions of costs, risks, benefits, alternative treatments, confidentiality, and study contact information. The consent will occur in the clinic room and in the presence of any caregivers who come to the visit. The research conversation will occur after the treating surgeon has evaluated the patient and deemed that individual a suitable candidate for hernia surgery and after the patient has accepted surgery as a treatment option. For individuals with dementia or other cognitive impairments, the consent will be conducted with the patient and caregiver. If no caregiver is present, then the patient will not be enrolled in the study. Additionally, the research assistant will emphasize to all patients that participation in the study is optional and deciding not to participate will not affect their clinical care. Patients will also be reassured that they can withdraw from the study at any time, and will

be provided a copy of the informed consent which contains contact information for the research team.

4.3.3 Enrollment of participants with cognitive impairment

Patients with known cognitive impairment or those identified by our baseline assessments will be included in the study. To optimize data collection, their identified caregivers will be asked to assist with completion of survey instruments and they will be contacted along with patients to prompt completion of all study visits. If caregivers assist with completion of any instruments, this will be noted in the research record.

4.3.4 Plan for optimizing recruitment and retention

At the time of enrollment, research assistants will collect information to facilitate multiple methods for contacting participants (phone, email, physical address) and will also obtain contact information for at least one caregiver, family member, or friend to use as a backup contact (VA medical records routinely include backup contact information). For each study visit after hospital discharge (see below), patients will receive an email and text reminder of their visit date 48 hours prior to the visit. Participants will also receive a $20 gift card upon completion of each study visit, and a $50 gift card if all visits are completed. To increase our likelihood of achieving the planned sample size, we will have weekly meetings via Microsoft Teams with graphical tracking of expected versus actual recruitment. We will also review the number of patients screened and reasons for non-enrollment of potential participants.

4.4 Randomization procedure

Randomized assignments will be generated ahead of time for each combination of strata and placed within stored and numbered envelopes kept at each hospital location. We will generate 20% more assignments than necessary to allow for potential withdrawals. Before patients are enrolled, physicians, patients, and research coordinators will not know which anesthesia modality will be assigned. Once patients are enrolled, the next envelope that applies to that participant (based on stratification factors) will be selected and labeled with the date and time of enrollment, the patient's name, and the research team member responsible for enrollment. The labeled and unopened envelope will be photographed for our records and the envelope number will be recorded in the participant's record.

Describe the method for identifying and recruiting candidates for the trial.
Describe procedures for documentation of reasons for ineligibility and for non-participation of eligible candidates (e.g. Screening Log).
Describe consent procedures, including any special requirements (e.g., consent for individuals who are unable to consent for themselves)
Describe the randomization procedure for assigning a participant to an intervention group.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

5.1.1 Local Anesthesia

Patients in the local anesthesia arm will receive an injection of a 50:50 mix of 1% lidocaine with epinephrine and 0.25% Marcaine at the surgical site (in the skin and subcutaneous layers + beneath the external oblique aponeurosis). Patients in the local arm will also receive intravenous sedation (propofol or Precedex) and pain medication (morphine or fentanyl) at the discretion of the attending anesthesiologist.

5.1.1.1 Standardizing use of local anesthesia for participating surgeons

To ensure that patients receive local anesthesia in a consistent way, all participating surgeons will undergo a training session for the technique of local injection. This will consist of practicing injection with a 50:50 mix of 1% lidocaine with epinephrine and 0.25% Marcaine into the skin at the incision site and the subcutaneous tissue down to the external oblique aponeurosis. The technique for surgical repair will be a standard Lichtenstein operation with the choice of mesh depending on the surgeon's preference. To verify that the appropriate procedure for injection of local anesthesia is being followed, the principal investigator or research assistants will observe each surgeon's first five cases and provide feedback.

5.1.1.2 Collaboration with anesthesia providers during surgery:

We have worked closely with anesthesia providers at both sites to formulate protocols for sedation during surgery. Anesthesia providers will refrain from using benzodiazepines prior to or during surgery given the known cognitive effects of that medication class on older adults. We will not otherwise mandate use of any particular agents for sedation or pain control, but expressed our preference for using propofol and fentanyl because of their short half-lives and limited side effect profile for older adults.

5.1.2 General anesthesia

General anesthesia will be administered at the discretion of the anesthesiologist and will involve a combination of inhaled and intravenous anesthesia.

5.1.3 Surgical technique

Open surgical repair will utilize the Lichtenstein tension-free repair with mesh. Choice of mesh will be at the discretion of the attending surgeon.

Indicate each study intervention, including how it is administered and the dosing schedule, as well as potential adverse effects. Indicate where the intervention will be administered (e.g., outpatient, exercise laboratory, intensive care unit). State guidelines for use of appropriate supportive care, medications or treatments.

Describe dose escalation procedures if relevant.

Include instructions for modifications to the study interventions, if appropriate and clearly explain modification of dose due to toxicity or any other reason. Address dose modifications for specific abnormal laboratory values of concern or other adverse events that are known to be associated with the planned intervention regimen.

For drug studies, package insert information can be referred to, but does not need to be included unless there is a new, significant change. Justify any aspects of the study that are not FDA-approved (e.g., different dosing schedule, new combination of drugs, new drug formulation).

5.2 Handling of Study Interventions

The medications necessary for administration of local and general anesthesia are available at the hospital from our pharmacy as part of routine care. Local anesthesia will be prepared by the surgical circulating nurse (not a member of the research team) in the operating room as is routinely done for clinical practice outside this trial.

The research assistants will be blinded to study allocation, as they will not be present during the operation and will only interact with patients before and after the operation. Due to the use of some IV medication (propofol or Precedex) for patients in the local arm, it will not necessarily be obvious postoperatively whether the patient had surgery under local or general anesthesia. Additionally, the incisions will be the same regardless of study arm and postoperative care will be identical.

Adverse reactions to any medications intraoperatively will be managed as described below.

For studies involving drugs and dietary or nutritional supplements, describe how these are to be acquired by the participating clinical sites (e.g., the pharmaceutical company will distribute the drug in bulk to the site pharmacist), and how they are to be stored, prepared, dispensed and, if applicable, how unused study products are destroyed or to be returned to the company supplying them.

Provide instructions for completing study intervention accountability records. If appropriate, reference the study Manual of Operations for detailed instructions on these issues.

For lifestyle/behavioral interventions, describe the intervention and general approach for delivering the intervention (e.g., manual describing procedures).

Note mechanisms (if any) for masking (i.e., blinding) study interventions. For example, if a placebo is being used in a drug trial, note whether it has similar color, taste, etc., as the active drug.

5.3 Concomitant Interventions

Allowed, required, and prohibited interventions (e.g., medications) will depend upon the study interventions and outcomes.

This section should be consistent with the medications and interventions restrictions in the inclusion/exclusion criteria.

5.3.1 Allowed Interventions

- Patients who develop an unexpected allergic reaction to either local or general anesthesia can be treated with antihistamines, epinephrine, and steroids according to standard hospital protocol.
- Patients who experience scrotal swelling postoperatively can be treated with ice packs and may undergo ultrasonography if there is suspicion for testicular injury. If testicular injury is found, urology service will be consulted for management.
- Patients who experience urinary retention (>200 mL of urine on bladder scan with inability to void) will undergo in and out catheterization followed by observation for up to 4 hours after. If they still demonstrate urinary retention at that time, they will be admitted to the hospital with placement of a Foley catheter and subsequent evaluation by urology.
- Patients with wound infections postoperatively will be managed by opening of the incision and administration of antibiotics, with or without readmission to the hospital.
- Patients who demonstrate malignant hyperthermia in response to general anesthesia will be treated with dantrolene and admission to the ICU for monitoring and resuscitation.
- Administration of IV fluids and IV or oral pain medications in the recovery area after surgery is permissible at the discretion of the attending anesthesiologist.

List all drugs and/or treatments/interventions that are allowed, including rescue medications, while on study.

5.3.2 Required Interventions

- All patients will be provided postoperative pain control consisting of 20 tablets of acetaminophen 300 mg / hydrocodone 5 mg, accompanied by 20 tablets of 10 mg bisacodyl to address constipation from opioids and anesthesia.

For example, if in weight loss study, vitamin pills may also be required.

5.3.3 Prohibited Interventions

- N/A

Include classes of medications, devices, etc. from the exclusion criteria (section 4.2) if they are also prohibited while the participant is on study. If necessary, provide a list of prohibited medications in appendix.

5.4 Adherence Assessment

We will review all operative and anesthesia records for cases of enrolled patients to verify the type of anesthesia that is administered and whether patients who start the operation under local anesthesia undergo a conversion to general anesthesia. Research assistants will also review cases with attending surgeons at the end of each operative day to identify any deviations from protocol. Any deviation from treatment assignment will then be recorded in the research record.

Adherence to a study regimen is generally defined as the extent to which participants take medications or comply with other study requirements as prescribed by the investigators. Define adherence (e.g., at least 80% of treatment intervention pills taken, 85% of exercise sessions attended). Provide details as to how adherence to study intervention will be assessed (e.g., pill counts, electronic monitoring devices, attendance at counseling sessions) and in the section on Data Analyses (Section 9.5), describe how this information will be incorporated into the analysis of the study results.

6 STUDY PROCEDURES

The Schedule of Evaluations in section 6.1 should include all study evaluations. Use an 'X' in a cell to indicate that a particular evaluation is to be performed at a particular study visit. The evaluations listed and their order in the table are only examples. The evaluations should reflect the protocol and should be arranged for clearest presentation. Additional columns may be needed to specify evaluations at intervention failure, at early discontinuation of study interventions, or at other special time points that require a different set of evaluations. In complicated studies with multiple study steps or multiple randomization points, it may be useful to include in the table the time of each step/randomization and the time that study intervention is given to the participant.

6.1 Schedule of Evaluations

Study evaluations are outlined in Table 1 (next page). Laboratory tests are limited to those obtained routinely as part of the preoperative evaluation so no additional labs/blood draws will be required as part of this study.

Assessment	Screening: Visit-1 (Initial Surgery Clinic Visit)	Baseline, Enrollment, Randomization: Visit 1 (Day 0: Initial Clinic Visit)	Treatment Visit 2 (During Surgery)	Treatment Visit 3 (After Surgery & Before Same Day Discharge)	Treatment Visit 4 (48 Hours After Surgery)	Treatment Visit 5 (2-Week Postoperative Visit)	Follow-Up: Final Visit (6-Month Postoperative Visit)
Informed Consent Form	X						
Demographics	X						
Medical & Surgical History	X						
General Physical Examination	X						
Current Medications	X						
Inclusion/Exclusion Criteria	X						
Blood Chemistries		X					
Hematology		X					
Urine Analysis		X					
Vital Signs		X	X	X		X	
Enrollment/Randomization		X					
Physical Function Assessment: Katz Index		X			X	X	X
Delirium & Cognitive Assessment: (1) Confusion Assessment Method short form, (2) Montreal Cognitive Assessment (5 minute version), (3) Trail Making Tests Parts A & B,		X		X	X	X	X
Frailty Assessment: Fatigue, Resistance, Ambulation, Illness and Loss of Weight Scale		X					
Pain Assessment: Visual Analog		X		X	X	X	X
Quality of Life: Carolinas Comfort Scale		X			X	X	X

Total Operating Room Time			X				
Time for Surgery			X				
Time in Post-Anesthesia Recovery Room				X			
Time in Step-Down Recovery Room				X			
Urinary Function/Unplanned Catheterization				X			
Unplanned Admission				X			
Adverse Events			X	X	X	X	X

6.2 Description of Evaluations

Descriptions for the Schedule of Evaluations define what is to be done at each study period and include special considerations or instructions for evaluations.

This section should include definitions of the column headings in the Schedule of Evaluations and any special instructions.

For studies collecting biological samples, describe the process for obtaining, processing and storing the samples. Include details on handling, preserving and shipping the specimens (e.g., required temperatures, location of storage, labeling).

6.2.1 Screening Evaluation and consent

These evaluations occur to determine if the candidate is eligible for the study.

Screening

Initial screening procedures will occur at least 24 hours prior to surgery and will be completed by research assistants. Screening procedures will determine whether the patient is the appropriate age and has a unilateral non-incarcerated inguinal hernia that has not previously been surgically repaired. This information will be obtained by reviewing the consult request, consult note, and prior medical records. The remainder of the screening (for patients found to be in the appropriate range, having unilateral and non-recurrent and non-incarcerated inguinal hernias) will occur at the time of the clinic visit when the participant is evaluated by the general surgery team. If patients are deemed to be candidates for surgery by the attending surgeon in clinic, then research assistants will obtain additional information on eligibility from the surgical team and approach potential participants as outlined below. All information necessary to determine eligibility will be available from the standard history and physical obtained by the surgical team as part of routine care for hernia patients. Research assistants will verify the information prior to enrollment.

Procedures

- Demographics: we will determine the participant's age, as this is one of our critical inclusion criteria.
- Medical & surgical history: we will verify that the patient has not had prior hernia surgery on the affected side and that he/she has no disqualifying medical conditions that would prevent the use of either local or general anesthesia.
- General physical examination: we will verify that the clinical team detected the presence of an inguinal hernia that is not incarcerated and does not require emergency surgery (strangulation or peritonitis).
- Current medications: we will verify the absence of medications that might cause adverse reactions with either general or local anesthesia.

Decision points regarding eligibility:

- Demographics: if patient age is <65 years old, they will not be eligible
- Medical & surgical history:
    - if the patient had prior hernia surgery on the affected side, then they will not be eligible
    - if the patient has a known allergy to local anesthesia or general anesthesia (or a reaction such as malignant hyperthermia), then they will not be eligible
    - If the patient has medical conditions that are relative or absolute contraindications to the use of general anesthesia or to surgery (heart failure with ejection fraction <20%, chronic obstructive pulmonary disease with a significant oxygen requirement, Child's C cirrhosis, any terminal disease with life expectancy < 6 months), then they will not be eligible
    - If the patient is taking any medication that might adversely interact with anesthesia and cannot be discontinued, then they will not be eligible

Specify allowable range of time prior to study entry during which all screening evaluations to determine eligibility must be completed. List and briefly describe all screening evaluations in bulleted format.

Include only those evaluations that are necessary to assess whether an individual meets enrollment criteria. Discuss the sequence of events that should occur during screening and the decision points regarding eligibility. List the time frame prior to enrollment within which screening tests and evaluations must be done. For example, DXA must be measured within 30 days of study enrollment.

Consenting Procedure

Potential participants will be identified by study research assistants 24-48 hours prior to their initial visit to the surgeon to discuss whether they will undergo hernia repair. We have obtained a waiver of informed consent from the IRB to review upcoming clinic records for this purpose. Once the consulting surgeon has determined that the patient needs surgery and the patient agrees to proceed with the operation, our research assistants will approach the patient to obtain consent for screening and study procedures (as a single consent form). At that time, the research assistant will explain the study purpose and discuss the potential risks/benefits of local anesthesia and general anesthesia, including the possibility of allergic reactions, heart attacks, stroke, blood clots, low blood pressure, pain, nausea, vomiting, and cognitive changes.

Patients who are not enrolled at the initial clinic visit may still be enrolled at subsequent preoperative visits as long as they occur at least 24 hours prior to surgery.

We will maintain records of informed consent as follows: a hard copy will be given to the patient and also stored in a secured filing cabinet in the PI's research office. We will also scan a copy

into the electronic medical record and store another scanned copy on our secure electronic research server. All informed consent forms will have a date and version number on the top right corner of all pages. The consent will include permission to contact participants by phone if needed to discuss any changes to the study protocol or other issues that occur during the trial.

Before any screening procedure is performed, informed consent must be obtained. Indicate whether there will be two consenting processes or a single informed consent form that describes both the screening and study procedures.

State which study staff will conduct the consent process and how it will be implemented.

Describe individual's education and informed consent process; any plan for review of consent document in case changes may be required; and how documentation of signed consent will be maintained by the study.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Enrollment is defined as the date that screening criteria are met and the individual agrees to participate and be randomized to either local or general anesthesia. The enrollment date will be recorded on the participant's case report form.

The act of enrolling a study participant should be defined. Since informed consent must be obtained if screening procedures are not a part of routine care, some studies use two informed consents: one for screening and one for enrollment. In this case the enrollment date is day the individual has met all the screening criteria and signs the second informed consent form.

Some studies utilize a single informed consent form that describes both screening and study procedures. In these studies enrollment is defined as the randomization date or as the date all of the screening criteria are met and the individual agrees to participate

In any case the enrollment date should be defined and recorded on a case report form along with the allowable window between screening and randomization.

Baseline Assessments

In addition to the information obtained as part of the screening evaluation, our research assistants will also obtain the following information:

- Laboratory evaluations: as part of the routine preoperative evaluation at our hospital sites, the following labs are obtained: blood chemistry, hematology/complete blood count, urine analysis. None of these labs will be ordered as part of our study, but we will record the information from this

routine screening in each patient's data file.

- Physical function assessment: we will administer the 6-item Katz index to measure independence in activities of daily living
- Delirium and cognitive assessment: we will administer a battery of tests to assess (1) cognitive function (overall and particular domains including processing, visual scanning, attention, mental set-shifting, executive function, and verbal memory) and (2) delirium risk
    - Confusion Assessment Method (short form)
    - Montreal Cognitive Assessment (5 minute version)
    - Trail Making Tests Parts A and B
- Frailty assessment: we will administer the 5-item Fatigue, Resistance, Ambulation, Illness, and Loss of Weight Scale to obtain a global measurement of frailty.
- Pain assessment: we will administer a 10-point visual analog scale to quantify pain levels related to the hernia
- Quality of life: we will use the 8-item Carolinas Comfort Scale to assess hernia-related quality of life
- Presence of symptoms indicating urinary retention (if not already identified by clinical team during history and physical)

For participants who have successfully been screened for eligibility and are enrolled into the study, baseline assessments are performed against which to measure the study outcome. They also ensure that the groups are balanced with respect to baseline characteristics. For example if the study hypothesis is "dietary intervention and exercise will reduce body weight by X% within one year", body weight will be assessed and documented.

List and briefly describe all baseline evaluations in a bulleted format.

Randomization

As outlined in section 4.4, randomization will occur immediately after screening and baseline assessment because the anesthesia team will need to be aware of the anesthetic plan prior to surgery, and the anesthesia team sees patients in their clinic after the surgical visit is complete. The study intervention (use of local or general anesthesia) will occur at the time of surgery, typically 4-6 weeks after the surgical clinic visit occurs and randomization is completed.

Randomization must precede intervention administration in a randomization study. Specify time window for (a) randomization relative to completion of screening and baseline and (b) initiation of study intervention relative to randomization.

6.2.3 Follow-up Visits

- Visit 2 (During Surgery)
    - The second set of assessments will occur during the normal course of clinical care for inguinal hernias (this does not represent an additional study visit on top of the usual care). During the surgery, the

anesthesiologist automatically records data on the below information as part of the routine anesthesia record.

- Vital signs: maximum, minimum, and median values for systolic and diastolic blood pressure and heart rate
- Total operating room time: the difference between the time the patient enters the operating room and the time the patient leaves the operating room
- Time for surgery: the time from the start of the operation (skin incision) and the end of the operation (skin closure)
- Adverse events, serious adverse events, and intraoperative complications
- Volume of fluids administered
- Minimum alveolar concentration of volatile anesthetic
- Dose of local anesthesia used

- Visit 3 (After Surgery & Before Same Day Discharge)
  - Inguinal hernia repair is typically an outpatient procedure where the patient is observed for several hours to ensure that there are no immediate complications of surgery or anesthesia and that patients are able to ambulate, tolerate oral intake, and manage basic self-care with assistance from family or other caregivers. From the time the patient leaves the operating room until the time the patient leaves the hospital, we will assess the following:
    - Vital signs: We will record any episodes of hypotension (mean arterial pressure <60) or hypertension (systolic blood pressure >180 or diastolic > 110), fever (temperature >101.6 F), tachycardia (heart rate >120), or poor oxygenation (oxygen saturation on pulse oximetry <85%). This information will be obtained from the post-anesthesia care unit and stepdown unit records.
    - Delirium and cognitive assessment: we will administer a battery of tests to assess (1) cognitive function (overall and particular domains including processing, visual scanning, attention, mental set-shifting, executive function, and verbal memory) and (2) delirium risk
      - Confusion Assessment Method (short form)
      - Montreal Cognitive Assessment (5-minute version)
      - Trail Making Tests Parts A and B
    - Time in post-anesthesia care unit: after surgery, all patients who had their operations performed under general anesthesia are observed in a unit with a nurse:patient ratio of ≤2:1, similar to intensive care units. This level of nursing care is required to quickly detect immediate complications of anesthesia, including respiratory failure and hypotension. Our research assistants will use the nursing records to determine what time the patient entered the unit and what time they were transferred to the next phase in care: the step-down unit. Patients having

surgery under local anesthesia are sent directly from the operating room to the step-down unit.
        - Time in step-down unit: Once general anesthesia patients meet criteria in the post-anesthesia care unit (awake, normal respiratory drive and blood pressure), they are transferred to the step-down unit. All local anesthesia patients are transferred directly to the step-down unit once their operation is complete. In this unit, patients are provided food and liquids to test their ability to tolerate oral intake. Patients also are asked to ambulate and void to ensure that they are capable of self-care and have not developed urinary retention. Our research assistants will use nursing records to identify the time of entry and departure from the step-down unit.
        - Urinary function/unplanned catheterization: research assistants will review nursing notes to determine whether patients were able to void or whether they required assistance. Our standard clinical protocol is that if patients have not urinated by 4 hours after surgery, they will undergo a bladder scan. If >200cc of urine is found in the bladder, the patients undergo in-and-out catheterization and are observed until they void again. If still unable to void, the patient has a foley catheter placed, is started on medication for prostatic hypertrophy, and arrangements are made with the urology service to undergo outpatient voiding studies and removal of the catheter within 1-2 weeks.
        - Unplanned admission: since most inguinal hernia surgeries are outpatient procedures, our nursing assistants will check the medical record the day after surgery to see if the patient was able to leave or was admitted. If admitted, we will contact the team to determine the reason for admission.
        - Adverse events and serious adverse events
- <u>Visit 4 (48 Hours After Surgery)</u>
    - Research assistants will contact the patient by phone to complete assessments. This may be completed at any time from 48 hours to 1 week after surgery.
    - Physical function assessment: we will administer the 6-item Katz index to measure independence in activities of daily living
    - Delirium and cognitive assessment: we will administer a battery of tests to assess (1) cognitive function (overall and particular domains including processing, visual scanning, attention, mental set-shifting, executive function, and verbal memory) and (2) delirium risk
        - Confusion Assessment Method (short form)
        - Montreal Cognitive Assessment (5-minute version)
        - Trail Making Tests Parts A and B
    - Pain assessment: we will administer a 10-point visual analog scale to quantify pain levels related to the hernia
    - Quality of life: we will use the 8-item Carolinas Comfort Scale to

assess hernia-related quality of life
    - Adverse events
- Visit 5 (2-Week Postoperative Visit)
    - Our standard clinical practice is to bring patients back to surgery clinic within 2-4 weeks of surgery to assess recovery and evaluate the incision. This assessment can take place any time in that 2-4 week postoperative period.
    - Vital signs
    - Physical function assessment: we will administer the 6-item Katz index to measure independence in activities of daily living
    - Delirium and cognitive assessment: we will administer a battery of tests to assess (1) cognitive function (overall and particular domains including processing, visual scanning, attention, mental set-shifting, executive function, and verbal memory) and (2) delirium risk
        - Confusion Assessment Method (short form)
        - Montreal Cognitive Assessment (5-minute version)
        - Trail Making Tests Parts A and B
    - Pain assessment: we will administer a 10-point visual analog scale to quantify pain levels related to the hernia
    - Quality of life: we will use the 8-item Carolinas Comfort Scale to assess hernia-related quality of life
    - Adverse events

Indicate treatment and follow-up visit assessments for each visit. List all measurements and procedures in bulleted format.

Include allowable time window in which evaluations may take place, e.g., study visits must be performed on the weeks indicated in the Schedule of Evaluations ± X days. The evaluation time window should be as narrow as technically feasible.

For example:

- *Visit 3:*
    - *Vital Signs*
    - *Treatment Administration Form*
    - *Concomitant Medications*
    - *Adverse Events*

- *Visit 6:*
    - *General Physical Examination*
    - *Vital Signs*
    - *Treatment Administration Form*
    - *Concomitant Medication*
    - *Adverse Events*

6.2.4 Completion/Final Evaluation

- The final evaluation/completion visit will be done by phone or video at 6 months after surgery, and can be performed any time from 6-9 months after the operation by research assistants
- Evaluations will include
    - Physical function assessment: we will administer the 6-item Katz index to measure independence in activities of daily living
    - Delirium and cognitive assessment: we will administer a battery of tests to assess (1) cognitive function (overall and particular domains including processing, visual scanning, attention, mental set-shifting, executive function, and verbal memory) and (2) delirium risk
        - Confusion Assessment Method (short form)
        - Montreal Cognitive Assessment (5-minute version)
        - Trail Making Tests Parts A and B
    - Pain assessment: we will administer a 10-point visual analog scale to quantify pain levels related to the hernia
    - Quality of life: we will use the 8-item Carolinas Comfort Scale to assess hernia-related quality of life
    - Adverse events or serious adverse events

List each assessment to be performed at the participant's final visit.

Specify evaluations needed for participants who discontinue study intervention early. Specify potential reasons for early termination. Specify any requirements (e.g., related to monitoring and reporting of adverse experiences) for follow-up on participants once they have stopped using the study intervention.

7 SAFETY ASSESSMENTS

Participant safety should be monitored once an individual is enrolled in the study. To assure comprehensive review of potential safety events, include an alphabetical list of expected adverse experiences for each study intervention, criteria for management and modification of the study intervention regimen or participant assessments if an adverse event occurs.

For investigational drug studies the section should identify toxicities that have been seen in previous studies.

7.1 Specification of Safety Parameters

Safety is a significant concern for our team. Overall, the risk for both arms is low, but there is potential risk both from surgery and anesthesia. At each study visit, we will actively examine for and inquire about possible adverse and serious adverse events. Specifically, we will monitor for the following to record in the adverse events database for review:

7.1.1 Definition of adverse events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32(a)).

7.1.2 Definition of serious adverse events (SAE)

A SAE is any event that results in death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when appropriate medical judgement indicates they may jeopardize the patient and may require medical or surgical interventions to prevent outcomes listed in this definition.

7.1.3 Definition of unanticipated problems (UP)

Unanticipated problems involving risks to participants or others include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency, given (1) the research procedures that are described in the protocol-related documents (IRB protocol or informed consent), and (2) the characteristics of the patients being studied
- Related or possibly related to participation in the research, where "possibly related" means there is a reasonable probability that the incident, experience, or outcome may have been caused by the research procedures
- Suggests the research places participants (or others) at a greater risk of physical, psychological, economic, social, or other harm than was previously known or recognized

7.1.4 SAE/AE potentially occurring with either local or general anesthesia

- Allergic reaction: if patients develop hives (raised red lesions) or a significant and persistent rash after administration of local or general anesthesia, this will be managed per the usual hospital protocol. Patients will receive a combination of epinephrine, corticosteroids, and antihistamines. Any patient with an allergic reaction will also be admitted for 24 hour observation that includes monitoring of vital signs, and blood pressure support with intravenous fluids. If the allergic reaction occurs during the operation, then the surgery will be canceled along with all assessments and will be rescheduled after it is determined that the operation can be performed safely without the allergic reaction.
- Hematoma or seroma: a collection of fluid in the tissues over the incision site or in the scrotum that is detected on physical exam constitutes either a seroma or hematoma. If minimal symptoms present, this will be managed by observation. If persistent and significant symptoms occur, the seroma/hematoma will initially be managed by aspiration under local anesthesia up to two times. If the symptoms persist after aspiration, then the patient can be taken back to the operating room for surgical evacuation.
- Infection: we define postoperative infections according to the National Surgical Quality Improvement Program definitions of superficial, deep, or organ space.[16] Infections will be managed by obtaining source control via opening the wound

and providing 10 days of oral antibiotics for infections not involving surgical mesh. If infections involve the mesh, then oral or intravenous antibiotics and may be attempted at the discretion of the attending surgeon versus mesh explantation.

- Injury to vessel: during dissection and/or mesh placement, there is the possibility of injury to the femoral or inferior epigastric vessels. If bleeding occurs at these vessels that cannot be resolved by applying pressure, this will be categorized as vascular injury. The inferior epigastric vessel is typically ligated without consequence if injured. Injury to femoral vessels will result in consult to vascular surgery for repair.
- Neuralgia/chronic pain: if patients experience pain at/near the site of surgery for >3 months after the operation, they are considered to have neuralgia. This will be managed initially by consultation with the pain service for injection of steroids and local anesthetic at the site for up to 3 times. If this proves unsuccessful, the patient will be considered for surgical neurectomy.
- Spermatic cord injury or orchitis: during surgical repair, the spermatic cord (including vas deferens, spermatic artery, venous plexus) are mobilized away from the hernia sac. If the surgeon identifies injury (division of the vas deferens, bleeding from artery or veins that requires intervention beyond holding pressure) or if there is involution of the testicle on the side of the surgery (identified by pain beyond the ordinary, swelling in the groin, ultrasound showing no flow) then we will categorize as a spermatic cord injury. Intraoperatively, a vas deferens injury will result in consultation of urology for repair. Arterial and venous injuries are generally too small to repair intraoperatively, but vascular surgery service can be consulted for evaluation. Postoperatively, there is no treatment for cord injury other than pain control, urologic evaluation, and possible removal of testicle on the injured side.
- Thromboembolic event: if patients develop deep venous thrombosis or pulmonary embolism from surgery, the diagnosis will be confirmed by the appropriate imaging tests (typically lower extremity ultrasound and CT of the chest) and treatment with anticoagulation (therapeutic heparin or Lovenox) will be immediately started. Patients will be admitted until they are clinically stable, and we will transition the patient to oral anticoagulation as soon as clinically feasible and arrange for evaluation by the hematology service for long-term follow-up and treatment. Additionally, any supportive care (oxygen, intravenous fluids, medications to support blood pressure) will be provided at the discretion of the treating team. Similarly, myocardial infarction and cerebrovascular accident will be treated by consulting specialists (cardiology or neurology) per the usual hospital protocol. These include anticoagulation and antiplatelet agents along with supportive care. Unless the patient becomes unable to complete study assessments, these complications would not result in changing the study schedule. If patients are unable to complete assessments during the specified time points, then that information would be missing for their records.

7.1.5 SAE/AE occurring only with general anesthesia

- Malignant hyperthermia: some patients can have a severe reaction to general anesthesia that includes a substantial increase in body temperature (sometimes as

high as 113° F) and rigid/painful muscles. If this occurs during surgery, the operation will immediately be stopped and patients will receive intravenous dantrolene. Patients will be admitted to the intensive care unit where they will continue to receive care including cooling blankets and fluids, oxygen, correction of electrolyte abnormalities, and standard medications to manage tachycardia and hypotension. We will also monitor kidney function and changes in creatinine kinase. The occurrence of this complication will not change the study intervention regimen or the schedule of participant assessments.

- Urinary retention: per our standard hospital protocol, if patients are unable to urinate by four hours after surgery, we will perform a bladder scan. If >200 mL of urine is seen, the patient will receive an in-and-out catheterization followed by observation for up to an additional four hours. If the patient is still unable to urinate, they will have a Foley catheter placed, be admitted for overnight observation, and be evaluated by urology. Typically, the patient goes home with a Foley leg bag and undergoes urodynamic testing 1 to 2 weeks later after being discharged with medication for benign prostatic hypertrophy. The occurrence of urinary retention will not change the study intervention regimen or the schedule of participant assessments.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

7.2.1 Assessing and recording

At each study visit, research assistants will actively elicit evidence of SAE and AE by asking questions related to symptoms and conducting physical exam in conjunction with the clinical team (which should be examining for these complications as well up to the 2 week postoperative time point). For the 6 month visit, symptoms will be elicited by asking questions via phone. At each time point, after reviewing the list of SAE and UE, an open-ended question will be asked regarding whether the patient is having any other additional problems or concerns. Any SAE/AE will be conveyed to the clinical team if not already identified, documented in the research record, and referred to the data safety and monitoring board immediately upon ascertainment. Information to be collected includes event description, time of onset, severity, relationship to study arm, and time of resolution/stabilization. All AE occurring during the study will be documented regardless of relationship to study assignment and all will be followed to adequate resolution

Any medical condition present at the time of screening will be considered as patient baseline and will not be reported as an AE. If the condition deteriorates during the study, it will be recorded as an AE. UP will be recorded in the research record throughout the study. Changes in severity of an AE will be recorded to allow an assessment of duration at each level of severity to be performed. AE found to be intermittent will have documentation of each episode onset and duration. We will record all events with start dates occurring after informed consent until 30 days after the last date of study participation.

7.2.2 Classification of AE

7.2.2.1 Severity

For AE not included in the protocol defined grading system, the following guidelines will be used to describe severity:

- Mild: requires minimal/no treatment and do not interfere with participant's daily activities
- Moderate: low level of inconvenience or concern with the therapeutic measures. May cause some interference with functioning.
- Severe: interrupt a participant's usual daily activity and may require systemic therapy or other treatment. Usually potentially life-threatening or incapacitating.

Other AE will be graded according to Common Terminology Criteria for Adverse Events version 5.0 severity.[17]

7.2.3 Relationship to study assignment

For all collected AE, the causality will be determined by the temporal relationship and clinical judgement of the assessor. The degree of certainty about causality will be graded as follows:

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an

alternative, definitive etiology documented by the clinician

7.3 Reporting Procedures

7.3.1 Adverse event reporting procedures

All AE will be reported to the IRB and NIA regularly and within 30 days of occurrence

7.3.2 Serious adverse event reporting procedures

Any occurrence that meets a protocol-defined SAE criterion will be submitted immediately (within 24 hours of identification) on an SAE form to the IRB and NIA. The principal investigators monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the investigator becomes aware of an SAE that is suspected to be related to study product, the investigator will report the event to the IRB and NIA.

All clinical trials must have a safety reporting system in place. Include details of the reporting procedures and time lines, including the individual responsible for each step (e.g., the Investigator, the Medical Monitor, etc.), how decisions will be made regarding determining relatedness and severity, which forms should be completed, (specific information on where to send this form is included), how reports will be distributed and what follow-up is required.

7.3.3 Unexpected event reporting procedures

All unanticipated problems will be reported to the IRB within five days of receiving notice of the event if the event requires immediate intervention to prevent serious harm to participants or others. All other unanticipated problems will be reported to the IRB as soon as possible and no later than ten business days from the date of the event or from the date the investigator is notified of the event.

Investigators will promptly report (according to the above schedule) the following events to the IRB if the events occur within 30 days of participants' active participation:

- Adverse events which in the opinion of the principal investigator are both unexpected and related to the study interventions.
- An unanticipated event related to the research that exposes individuals other than the research participants (e.g., investigators, research assistants, public, etc.) to potential risk
- Information that indicates a change to the risks or potential benefits of the research.
- An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than initially presented to the IRB.
- A paper is published from another study that shows that the risks or potential

benefits of your research may be different than initially presented to the IRB.
- A breach of confidentiality.
- Incarceration of a participant in a protocol not approved to enroll prisoners.
- Change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant.
- Complaint of a participant when the complaint indicates unexpected risks or cannot be resolved by the research team.
- Protocol violation (accidental or unintentional change to the IRB approved protocol) that harmed participants or others or that indicates participants or others may be at increased risk of harm.
- Any other event that indicates participant or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

7.4 Follow-up for Adverse Events

AEs will be followed until resolution even if this extends beyond the study-reporting period. Resolution of an AE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Describe how AEs will be followed until resolved or considered stable. Specify duration of follow-up.

7.5 Safety Monitoring

The NIA Guidelines on Data and Safety Monitoring generally require that a NIA-appointed Data and Safety Monitoring Board or Safety Officer monitor clinical trials. Please see the Safety Monitoring Guidelines (a link will be inserted here).

Inguinal hernia repair is generally considered a safe procedure with very few (<1% risk of SAE).[3,7,8] Both local and general anesthesia are considered reasonable standard of care for the operation, and there are generally few AE or SAE resulting directly from the anesthesia modality. Most complications, AE, SAE, or UP result from the surgery rather than anesthesia, and the surgical technique is the same for both study arms. Consequently, we will convene our data safety and monitoring board to review all AE, SAE, and UP once 50% of expected enrollment is obtained. The UT Southwestern Department of Surgery maintains a standing DSMB for monitoring of all trials in our department. Given that all published studies of local versus general anesthesia have been completed without significant rates of adverse events or early termination, it is highly unlikely that the use of stopping rules will be required.

8 INTERVENTION DISCONTINUATION

The study will be halted if three grade 3 AEs are identified and determined to be probably related or definitely related to the study interventions (distinct from surgical complications). The PI will notify NIA and the IRB immediately when the third grade 3 event is reported, and enrollment screens will stop accepting new study participants.

Participants may voluntarily withdraw/stop participation at any time and for any reason (noted on consent form). If participants withdraw, we will make every effort to obtain permission and convince them to complete planned evaluations and will try counseling patients to re-enroll in the study if possible. We will also make every effort to continue monitoring and treating AE/SAE for participants who withdraw.
There will be no replacement of participants who withdraw early. Additionally, we will continue to follow participants, with their permission, even if the study intervention is discontinued.

List criteria for discontinuing the study intervention/product (e.g., development of toxicities, study closure by institute) for a participant and methods for determining when criteria are met.

If relevant, include criteria for temporary discontinuation of treatment and define its length.

Also note that subjects may withdraw voluntarily from participation in the study at any time and for any reason. Participants should continue to be followed, with their permission, even if the study intervention is discontinued. Discuss any modifications to the schedule and duration of continued follow-up and indicate the evaluations to be completed while the participant is either temporarily or permanently discontinued from study intervention but followed for outcomes, if applicable.

This section should also include a discussion of replacement of subjects who discontinue early, if replacement is allowed.

Note: It is vital to collect safety data on any subject discontinued due to an AE or SAE. In any case, every effort must be made to undertake protocol-specified safety follow-up procedures. If voluntary withdrawal occurs, the subject should be asked to continue scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any AE resolve or the subject's condition becomes stable.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

9.1.1 General approach

This is a two-arm (parallel) pilot randomized trial where adults aged 65 years and older are assigned to have their inguinal hernias repaired under either local (arm 1) or general anesthesia (arm 2).

9.1.2 Central hypothesis

The overarching hypothesis driving design of this study is that performing inguinal hernia surgery under local rather than general anesthesia for patients aged 65 years and older will

significantly reduce operative and recovery time, will lead to fewer complications, and will lead to better cognitive and physical recovery from surgery. This hypothesis will eventually be tested in a multisite randomized trial whose design will be informed by this pilot randomized trial.

The hypothesis for this pilot study is that we will be able to successfully recruit, randomize, and retain enough patients for a fully powered multisite randomized trial. Additionally, we plan to test study procedures for screening, enrollment, randomization, outcome measurement, and retention while also evaluating whether we can reduce the study burden by eliminating some of the study instruments. We also hypothesize that, although the pilot study (by definition) is not powered to detect differences between groups, that the local anesthesia group will have fewer complications and better physical and cognitive function (though the difference may not be statistically significant).

9.1.3 Justification for pilot design

The chances of completing a successful multisite randomized clinical trial are increased by testing study procedures and processes on a smaller scale prior to conducting a fully powered trial.[18,19] This will enable us to identify and address problems prior to initiating the fully powered study. Conducting a pilot study also allows us to test study instruments and potentially reduce the time burden at each evaluation visit by determining whether study measures are statistically redundant (the other measures explain a substantial portion of one measure's variance). Reducing the time burden for participants is an important step to enhance the completeness of data collection by minimizing missing data and reducing withdrawals from the study.

As outlined below and in the attached grant proposal, data from the pilot study will also be used for preliminary estimation of effect sizes for the future randomized trial. As the pilot is, by definition, not fully powered to detect all relevant differences between groups, this analysis is entirely exploratory.

9.1.4 Primary outcomes and hypotheses

1) Outcome: Rates of enrollment
    a. Hypothesis: Based on our preliminary data, at least 75% of eligible patients will agree to be randomized.
2) Outcome: Proportion of participants completing all study visits
    a. Hypothesis: We will be able to follow 100% of patients up to their 2 week postoperative visit (as essentially all patients keep this appointment in our clinical practice), and we will be able to follow at least 90% of patients at the six month time point.
3) Outcome: Proportion of missing data
    a. Hypothesis: Missing data on study instruments will be <5%
4) Outcome: Time to complete study evaluations and instruments
    a. Hypothesis: Total time to complete each study evaluation will be acceptable to patients and <30 minutes.
5) Outcome: Participant satisfaction with study procedures and instruments
    a. Hypothesis: Overall time burden for instrument completion will be acceptable to patients

6) Outcome: Whether survey instruments can be eliminated due to redundancy
    b. Hypothesis: One or more study instruments can be eliminated (thus reducing the time burden) because the other instruments may predict a substantial portion of variance
(7) Outcome: Estimate sample size for fully powered randomized trial.
    a. Hypothesis 1: Using data from the pilot study, we will be able to establish stable estimates of the necessary sample size for a randomized trial.
    b. Hypothesis 2: We will be able to identify the optimal primary outcome for a multisite randomized trial by balancing the necessary sample size needed to adequately power the study versus the clinical significance of each outcome.

9.1.5 Secondary outcomes and hypotheses

Again note that this pilot trial is not powered to detect differences in the secondary (clinical) outcomes described below. Our hypotheses reflect expected findings for a larger, multisite randomized clinical trial that will follow this pilot study.

1) Outcome: Quality of life
    a. Hypothesis: quality of life will be significantly improved when older adults have their inguinal hernias repaired under local rather than general anesthesia.
2) Outcome: Physical function
3) Hypothesis: physical function (activities of daily living) will be significantly improved when older adults have their inguinal hernias repaired under local rather than general anesthesia.
4) Outcome: Cognitive function
    a. Hypothesis: Cognitive function will be significantly improved when older adults have their inguinal hernias repaired under local rather than general anesthesia.
5) Outcome: Pain
    a. Hypothesis: Pain will be similar for older adults having hernia surgery regardless of anesthesia modality.
6) Outcome: Postoperative complications
    a. Hypothesis: The overall incidence of postoperative complications will be significantly reduced when older adults have their inguinal hernias repaired under local rather than general anesthesia. This will mostly be due to decreased rates of urinary retention (a common complication of general anesthesia).
7) Outcome: Operative and anesthesia times
    a. Hypothesis: Time for surgery (incision to closure) and anesthesia (enter to exit operating room) will be significantly decreased when older adults have their inguinal hernias repaired under local rather than general anesthesia.
8) Outcome: Recovery time (time spent in the post-anesthesia care and stepdown units)
    a. Hypothesis: Time spent in the post-anesthesia care and stepdown units after surgery will be significantly decreased when older adults have their inguinal hernias repaired under local rather than general anesthesia.

State the statistical hypotheses.

Describe the reasons for choice of study design (e.g., parallel groups, crossover, immediate versus deferred intervention, factorial, large simple trial, equivalency or non-inferiority trial); why certain design features were chosen (e.g., for a crossover trial, how the length of the washout period was chosen).

Describe the primary and secondary hypotheses and the primary and secondary outcome measures as well as their validity and reliability.

9.2 Sample Size and Randomization

Describe sample size calculation and effect size with respect to power. Specify the test statistic; Type I and Type II error rates; assumed event rate event rate for dichotomous outcome (mean and / or variance for continuous outcome) for each study arm; assumed rates of drop-out, withdrawal, cross-over to other study arms, missing data, etc.; and approach to handling withdrawals and protocol violations, in terms of an "intent to treat" approach.

9.2.1 Treatment Assignment Procedures

We will randomly assign older patients having inguinal hernia surgery to one of the two study arms: (1) local anesthesia or (2) general anesthesia. Our goal for enrollment will be a total of 80 participants with 40 participants in each arm and a total of 40 participants from each site. We will use a stratified randomization scheme with blocking within strata. Stratification factors include hospital location (Dallas or Houston) and age (65-75 or 75+ years). Equal allocation by strata will be used so that differences among hospitals and age groups will be balanced. Randomized assignments will be generated ahead of time for each combination of strata and placed within stored and numbered envelopes kept at each hospital location. We will generate 20% more assignments than necessary to allow for potential withdrawals. Before patients are enrolled, physicians, patients, and research coordinators will not know which anesthesia modality will be assigned. Once patients are enrolled, the next envelope that applies to that participant (based on stratification factors) will be selected and labeled with the date and time of enrollment, the patient's name, and the research team member responsible for enrollment. The labeled and unopened envelope will be photographed for our records and the envelope number will be recorded in the participant's record.

9.2.1 Masking treatment assignment

Although the patient and operating team (surgeon, anesthesiologists, nurses) will unavoidably be aware of which study arm participants are assigned to, the investigative team will remain blinded to treatment assignment at all times. Research assistants collecting baseline, peri-, and postoperative outcomes will be blinded to study assignment when conducting their assessments. For the baseline assessment, the research assistant will not open the envelope containing the treatment assignment until the baseline assessment is complete. For subsequent assessments, a different research assistant will interact with the patient. The investigator and study team will also be blinded to treatment assignment until after data analysis is complete, with the exception of the statistician (Dr. Reisch) who will be analyzing the data. All study results will be presented to the investigator and DSMB with patients identified as belonging to "group A" or "group B"

and the assignment will remain masked until the final analysis is complete and the findings are ready for publication.

9.2.2 Sample Size

There is no widely accepted method for estimating statistical power for a pilot study since, by definition, it is not powered to detect significant differences between groups. Instead, the goal is to demonstrate feasibility of conducting a fully powered trial and to provide some baseline information that can assist with estimation of the final sample size for the multisite trial. However, our sample size of 80 patients over 2 years (20 patients per site per year) does provide 80% power at $\alpha < 0.05$ for a 30 minute difference in operative and recovery time, assuming a common standard deviation of 45 minutes and a total operating + post-anesthesia unit time of 180 minutes for the general anesthesia group (consistent with our preliminary data). We would also have 80% power to detect a 5-point difference in quality of life on the Carolinas Comfort Scale, given prior published data on this instrument.[20,21] Additionally, we generated 1000 bootstrap samples using data from our prior retrospective study comparing local versus general anesthesia for hernia repair. Each sample contained 40 patients who had surgery under local anesthesia and 40 under general anesthesia. We then evaluated the range of estimated mean and standard deviation for total operative and recovery time across all 1000 samples and found that the mean range (156-205 minutes) and standard deviation (42-113) provided reasonable and stable estimates for the actual values in the original sample. This provides further evidence that a sample size of 80 patients would provide reasonable data for estimating sample size for a fully powered multisite randomized trial.

Describe the treatment assignment procedures (randomization, minimization, relevant criteria, etc). If such procedures are proposed describe rationale as well as the procedure.

Plans for the maintenance of trial randomization codes and maintaining appropriate masking for the study should be discussed, including the timing and procedures for planned and unplanned breaking of randomization codes should be included. Include a statement regarding when unmasking may occur and who may unmask.

If the randomization will be stratified, indicate whether (and why) there is a sample size goal for each stratum. Identify what factors (if any) will be used to stratify the randomization.

9.3 Interim analyses and Stopping Rules

Since the overall safety of both general and local anesthesia have long been established and both techniques are considered reasonable standard of care, we plan for a single interim analysis once 50% enrollment is reached. We will not employ formal stopping rules, given the incredibly low likelihood of this necessity. However, as outlined above, we will temporarily halt enrollment if 3 AE occur so that we can identify potential causes before proceeding.

If an interim analysis is planned, describe the rationale, effect on "spending" the Type I error, and method for adjusting calculations. As relevant, provide guidelines for stopping the study for reasons of efficacy, safety, futility, or poor study performance (e.g., slow accrual, high losses-to-follow-up, and poor quality control).

Describe safety findings and statistical rules that would temporarily suspend enrollment and/or study intervention until a safety review is convened (either routine or ad hoc) to determine whether the study should continue per protocol, proceed with caution, be further investigated, be discontinued, or be modified and then proceed.

Examples of findings that might trigger a safety review are the number of SAEs overall, the number of occurrences of a particular type of SAE, severe AEs/reactions, or increased frequency of events. Such findings are presented to the study statistician or to the Data and Safety Monitoring Board (DSMB) statistician to review the events by group to determine whether there are statistical as well as clinical concerns. The statistician reports his findings to a closed session of the DSMB or to the Safety Officer and/or NIA. The findings are used to determine what steps will be taken.

9.4 Outcomes

Discuss how the outcomes will be analyzed. Describe whether the documentation of an outcome will be reviewed and adjudicated by a committee, how quickly the committee will perform the adjudication, and whether the committee will be masked to the participant's intervention group assignment.

9.4.1 Primary outcomes

The primary outcomes are all pilot outcomes designed to demonstrate feasibility of conducting a multisite randomized clinical trial. The pilot outcomes, methods for measurement, and timing of measurement are outlined in Table 2 (page 40).

1) Outcome: Rates of enrollment and percentage of eligible patients enrolled
    a. Measurement: Each week, research assistants will compile running counts of patients who are screened, found eligible, and enrolled. Reasons for non-enrollment will be recorded. The measured outcomes will also be placed in graphical format to plot a comparison of expected versus actual rates for eligibility and enrollment.
    b. Timing: The reports of numerical and graphical values will be reviewed every other week at our videoconference (Teams) team meeting that will include both study sites.
2) Outcome: Proportion of participants completing all study visits
    a. Measurement: Research assistants will maintain running counts of participants who complete each study visit. We will evaluate rates of completing (attending) each study visit and calculate the final proportion of patients who complete all visits. This will be presented to the study team in numerical and graphical format
    b. Timing: Reports will be reviewed at each every other week study team meeting.
3) Outcome: Proportion of missing data
    a. Measurement: For each visit, every study instrument will be entered into our electronic database and missing items will have a separate code number (-

99) to facilitate easy counting of missing items vs total items to complete. Research assistants will generate a report showing overall percentage of missing data (number of missing items/current number of possible items for each patient) and the percent of missing data for each patient.

b. Timing: Each bi-weekly team meeting will involve a review of missing data at the overall study and patient level.

4) Outcome: Time to complete study evaluations and instruments
    a. Measurement: Research assistants will time participants while completing each study research form and will also time the entire encounter at each study visit.
    b. Timing: Data will be collected at each visit and will be reviewed by the study team at the last team meeting of each month to establish reasonably stable estimates of time.
5) Outcome: Participant satisfaction with study procedures and instruments
    a. Measurement: At each visit, after completing all other study forms and procedures, participants will be asked to complete a brief 10-item Likert-type score to measure overall satisfaction with the study visit and a similar item assessing satisfaction with the time burden of the instruments. Additionally, we will conduct a brief interview with open-ended questions at the end of each visit asking patients to provide any feedback on the study procedures or instruments. These will not be recorded but field notes by the research assistant will be taken.
    b. Timing: Assessments will occur at each study visit and will be reviewed at the last team meeting of each month.
6) Outcome: Whether survey instruments can be eliminated due to redundancy
    a. Measurement: To determine whether we can reduce the survey burden by eliminating redundant measures, we will employ methods outlined by Harrell for data reduction.[22] Each survey instrument will be evaluated as the dependent variable in a separate linear regression with the scores of all other instruments used as predictors, along with demographic information. The adjusted R^2 (explained variance) for each regression will be estimated. Any instrument where the R^2 exceeds 40% will be eliminated based on the idea that little additional information is provided by including that instrument (i.e. the other surveys explain a substantial portion of the information contained within that instrument).
    b. Timing: We will assess survey redundancy once 25% of planned enrollment is achieved and we will measure again at 75% enrollment. This will provide reasonable data stability for estimation and also provide time for us to test study procedures after eliminating any instruments that are found to be redundant.
7) Outcome: Estimating sample size for fully powered trial
    a. Measurement: For continuous variables, we will estimate means and standard deviations. For categorical variables, we will estimate proportions and 95% confidence intervals.
    b. Timing: Final sample size estimate will be performed after data collection for the last patient is complete.

Table 2. Analysis of primary (pilot) outcomes		
Outcome	**Measurement**	**Timing**
Rate of enrollment and percent of eligible patients enrolled	• Running count and graph of planned versus actual enrollment	Team meeting (every other week)
Reasons for non-enrollment	• Running count and graph	Team meeting (every other week)
Proportion of participants completing all visits	• Running count and graph	Team meeting (every other week)
Proportion missing data	• Running count and graph	Team meeting (every other week)
Time to complete study evaluations and instruments	• Research assistant uses timer during visit	Once per month at team meeting
Participant satisfaction with procedures and instruments	• 10-point Likert-type scale • Short interview at end of each visit	Once per month at team meeting
Identify redundant instruments	• Predict explained variance (R-squared) of each instrument from scores of other instruments	At 25% and 75% enrollment
Identify areas of improvement for study procedures	• Short patient interview at end of each visit • Study team discussions at weekly meeting	Team meeting (every other week)
Estimate sample size	• Measures of dispersion (mean and standard deviation) • Proportions and 95% confidence intervals	After data collection for final patient is complete

State and define the primary outcome measure and specify at which study visit the outcome assessments will be performed.

9.4.2 Secondary outcomes

Timing of measurements for secondary outcomes is outlined in the schedule of evaluations (section 6.1). Instruments are briefly summarized in Table 3 below.

1) Outcome: Quality of life
    a. Measurement: The Carolinas Comfort Scale (CCS) was developed specifically to measure quality of life in patients having hernia repair.[23] The instrument consists of 8 items on a 6-point Likert-type scale. The Cronbach's alpha was 0.979 in the original development paper and 0.95 on a subsequent international validation study.[21] The CCS demonstrates superior discrimination when compared to generic quality of life instruments (SF-36), with reasonable test-retest reliability (kappa coefficients for questions range from 0.40-0.60 for all but 1 item. Additionally, the CCS is used as the primary quality of life instrument for the International Hernia Mesh Registry because it can be rapidly administered, is well accepted by patients, is highly reliable, and typically has only 10-15% missing data when used for the international registry.[21] The CCS can be scored as a summary of all items and as a binary score for the presence or absence of symptoms. We will use a 0.5 standard deviation difference on the continuous scale as the minimal clinically important difference.[24]
    b. Timing: The CCS will be measured at baseline, 48 hours after surgery, at 2 weeks after surgery, and at 6 months after surgery.
2) Outcome: Physical function
    a. Measurement: We will measure independence in activities of daily living with the 6-item Katz Index, a long-established measure for physical/functional status for individuals expected to have at least some degree of disability.[25] Prior work demonstrates coefficients of scalability ranging from 0.74-0.88, indicating the Katz Index offers a useful cumulative scale.[25] We will score the instrument on a 0-6 scale, indicating the number of activities where the participant is partially or fully dependent. A 0.5 standard deviation difference will again represent the minimal clinically important difference.[24]
    b. Timing: Measurement will occur at baseline, at 2 weeks after surgery, and at 6 months after surgery.
3) Outcome: Cognitive function and delirium
    a. Measurement
        i. Confusion Assessment Method (CAM) short form: The CAM is the most widely used instrument for detection of delirium, with typical sensitivity of 94% and specificity of 89% across multiple studies.[26] The instrument is scored on a 7-point scale and we will consider a 0.5 standard deviation difference as the minimal clinically significant difference.[24] Items include evaluation of attention, disorganized thinking, and altered levels of consciousness.
        ii. Montreal Cognitive Assessment (MoCA) 5-minute form: The MoCA is a widely used tool for detection of dementia and other cognitive impairment, and is sensitive when used as a global cognitive screening tool.[27] The 5-minute form was developed to (1) reduce the significant time burden of the longer version which typically takes 15 minutes to complete, while (2) maintaining the psychometric advantages of the longer form, and (3) facilitating assessment by

telephone rather than in-person interviews. The instrument evaluates memory/attention, language fluency, orientation, and recall. The 5-minute MoCA has strong correlation with the full version (r=0.87), maintains the discrimination of the full version (area under the curve 0.78 versus 0.75 for full version, p>0.05), and has strong test-retest validity (intraclass correlation coefficient 0.89).[27] Since the 5-minute MoCA was also developed for testing by phone or in person, it meshes with our protocol plans to conduct immediate and long-term follow up by phone. A difference of 3 points is typically considered clinically significant.[27]

iii. Trail Making Tests Parts A and B: The Trail Making Test is one of the most popular neuropsychological tests for detecting processing speed, attention, and visual scanning.[28] Part A requires participants to draw a line between circles containing numbers, and the circles must be connected in numerical order. Part B is similar, but alternates letters and numbers (1, A, 2, B, et). Both items are scored as time to completion and then normalized to population data based on age and education.[28] To address ceiling effects on Part B, we will use the efficiency score for individuals who do not complete the instrument in <300 seconds.[29] A 0.5 standard deviation difference in time is considered clinically significant.[28]

b. Timing: All measures will be administered at baseline, prior to discharge, at 48 hours after discharge, at 2 weeks after surgery, and at 6 months after surgery

4) Outcome: Pain
   a. Measurement: We will use a 10-point visual analog scale to measure overall pain levels. A 0.5 standard deviation will be considered a clinically significant difference.
   b. Timing: Overall pain will be measured at baseline, prior to discharge, at 48 hours after surgery, at 2 weeks from surgery, and at 6 months from surgery.
5) Outcome: Postoperative complications
   a. Measurement: All complications will be recorded based on VA Surgical Quality Improvement Program definitions.[30] For complications not defined in VASQIP, definitions are also provided below.
      i. Allergic reaction: if patients develop hives (raised red lesions) or a significant and persistent rash after administration of local or general anesthesia, this will be managed per the usual hospital protocol. Patients will receive a combination of epinephrine, corticosteroids, and antihistamines. Any patient with an allergic reaction will also be admitted for 24 hour observation that includes monitoring of vital signs, and blood pressure support with intravenous fluids. If the allergic reaction occurs during the operation, then the surgery will be canceled along with all assessments and will be rescheduled after it is determined that the operation can be performed safely without the allergic reaction.
      ii. Hematoma or seroma: a collection of fluid in the tissues over the

incision site or in the scrotum that is detected on physical exam constitutes either a seroma or hematoma. If minimal symptoms present, this will be managed by observation. If persistent and significant symptoms occur, the seroma/hematoma will initially be managed by aspiration under local anesthesia up to two times. If the symptoms persist after aspiration, then the patient can be taken back to the operating room for surgical evacuation.

iii. Injury to vessel: during dissection and/or mesh placement, there is the possibility of injury to the femoral or inferior epigastric vessels. If bleeding occurs at these vessels that cannot be resolved by applying pressure, this will be categorized as vascular injury. The inferior epigastric vessel is typically ligated without consequence if injured. Injury to femoral vessels will result in consult to vascular surgery for repair.

iv. Neuralgia/chronic pain: if patients experience pain at/near the site of surgery for >3 months after the operation, they are considered to have neuralgia. This will be managed initially by consultation with the pain service for injection of steroids and local anesthetic at the site for up to 3 times. If this proves unsuccessful, the patient will be considered for surgical neurectomy.

v. Spermatic cord injury or orchitis: during surgical repair, the spermatic cord (including vas deferens, spermatic artery, venous plexus) are mobilized away from the hernia sac. If the surgeon identifies injury (division of the vas deferens, bleeding from artery or veins that requires intervention beyond holding pressure) or if there is involution of the testicle on the side of the surgery (identified by pain beyond the ordinary, swelling in the groin, ultrasound showing no flow) then we will categorize as a spermatic cord injury. Intraoperatively, a vas deferens injury will result in consultation of urology for repair. Arterial and venous injuries are generally too small to repair intraoperatively, but vascular surgery service can be consulted for evaluation. Postoperatively, there is no treatment for cord injury other than pain control, urologic evaluation, and possible removal of testicle on the injured side.

vi. Urinary retention: per our standard hospital protocol, if patients are unable to urinate by four hours after surgery, we will perform a bladder scan. If >200 mL of urine is seen, the patient will receive an in-and-out catheterization followed by observation for up to an additional four hours. If the patient is still unable to urinate, they will have a Foley catheter placed, be admitted for overnight observation, and be evaluated by urology. Typically, the patient goes home with a Foley leg bag and undergoes urodynamic testing 1 to 2 weeks later after being discharged with medication for benign prostatic hypertrophy. The occurrence of urinary retention will not change the study intervention regimen or the schedule of participant assessments.

vii. Reoperation: Any unplanned surgery after the participant leaves the operating room following repair of the hernia.
viii. Unplanned readmission or emergency room visit: Any admission for a planned outpatient surgery, or any hospital admission or emergency room visit that occurs after discharge.
ix. Cardiac arrest requiring cardiopulmonary resuscitation: The absence of cardiac rhythm or presence of chaotic cardiac rhythm that results in loss of consciousness requiring the initiation of any component of basic and/or advanced cardiac life support.
x. Myocardial infarction: A new transmural acute myocardial infarction occurring during surgery or within 14 days following surgery as manifested by new Q-waves on ECG.
xi. Cerebral vascular accident/stroke: Patient develops an embolic, thrombotic, or hemorrhagic vascular accident or stroke with motor, sensory, or cognitive dysfunction (e.g., hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) that persist for 24 or more hours.
xii. Peripheral nerve injury: Peripheral nerve damage may result from damage to the nerve fibers, cell body, or myelin sheath during surgery. Peripheral nerve injuries (e.g., motor, sensory, and mixed motor/sensory injury) to the cervical plexus, brachial plexus, ulnar plexus, lumbar-sacral plexus (sciatic nerve), perineal nerve, and/or the femoral nerve should be included.
xiii. Clostridium difficile infection: C. difficile-associated disease occurs when the normal intestinal flora is altered, allowing C. difficile to flourish in the intestinal tract and produce a toxin that causes a watery diarrhea. C. difficile diarrhea is confirmed by the presence of a toxin in a stool specimen. Answer yes only if you have a positive culture for C. difficile with a toxin assay and/or diagnosis of C. difficile documented in the chart.
xiv. Bleeding requiring >4 units packed red blood cells
xv. Deep vein thrombosis: The identification of a new blood clot or thrombus within the venous system, which may be coupled with inflammation. This diagnosis is confirmed by a duplex, venogram or CT scan. The patient must be treated with anticoagulation therapy, and/or placement of a vena cava filter or clipping of the vena cava.
xvi. Pulmonary embolism: Lodging of a blood clot in a pulmonary artery with subsequent obstruction of blood supply to the lung parenchyma. The blood clots usually originate from the deep leg veins or the pelvic venous system. Enter "YES" if the patient has a V-Q scan interpreted as high probability of pulmonary embolism or a positive pulmonary arteriogram or positive CT scan. Treatment usually consists of: (a) Initiation of anticoagulation therapy, (b) Placement of mechanical interruption (e.g. Greenfield Filter), for patients in whom anticoagulation is contraindicated or already instituted.
xvii. Systemic sepsis: If the primary physician or the chart states that the

patient had systemic sepsis within the 30 days postoperatively, choose from the following choices for sepsis. If neither is present follow these definitions and choose the most applicable: (1) Sepsis: Definitive evidence of infection, plus evidence of a systemic response to infection. This systemic response is manifested by TWO or more of the following conditions: Temp >38 degrees C or <36 degrees Celsius; Septic Shock: Sepsis with hypotension despite adequate fluid resuscitation combined with perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured. HR >90 bpm, RR >20 breaths/min or PaCO2 <32 mmHg(<4.3 kPa), WBC >12,000 cell/mm3, <4000 cells/mm3, or >10% immature (band) forms

xviii. Prolonged ileus: Ileus is obstruction of the intestines from a variety of causes including mechanical obstruction, peritonitis, adhesions, or post-surgically as a result of functional dysmotility by the bowel. Bowel obstruction is any hindrance to the passage of the intestinal contents. Prolonged ileus or obstruction is defined as longer than 5 days postoperatively.

xix. Pneumonia: Inflammation of the lungs caused primarily by bacteria, viruses, and/or chemical irritants, usually manifested by chills, fever, pain in the chest, cough, purulent, bloody sputum. Enter "YES" if the patient has pneumonia meeting the CDC definition of pneumonia below AND pneumonia not present preoperatively. Pneumonia must meet one of the following TWO criteria: Criterion 1. Rales or dullness to percussion on physical examination of chest AND any of the following: a. New onset of purulent sputum or change in character of sputum, b. Organism isolate from blood culture, c. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy OR Criterion 2. Chest radiographic examination shows new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following: a.New onset of purulent sputum or change in character of sputum, b.Organism isolated from the blood, c.Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy, d. Isolation of virus or detection of viral antigen in respiratory secretions, e. Diagnostic single antibody titer (IgM) or fourfold increase in paired serum samples (IgG) for pathogen, f.Histopathologic evidence of pneumonia

xx. Failure to wean off ventilator or reintubation within 48 hours: If the patient remains intubated following completion of surgery for a period of ≥48 hours or is reintubated within 48 hours of surgery completion.

xxi. Urinary tract infection: Postoperative symptomatic urinary tract infection must meet one of the following TWO criteria from the

CDC definition:

1. One of the following: fever (>38 degrees C), urgency, frequency, dysuria, or suprapubic tenderness AND a urine culture of > 105 colonies/ml urine with no more than two species of organisms OR

2. Two of the following: fever (>38 degrees C), urgency, frequency, dysuria, or suprapubic tenderness AND any of the following:

- Dipstick test positive for leukocyte esterase and/or nitrate
- Pyuria (>10 WBCs/cc or > 3 WBC/hpf of unspun urine)
- Organisms seen on Gram stain of unspun urine
- Two urine cultures with repeated isolation of the same uropathogen with >102 colonies/ml urine in non-voided specimen
- Urine culture with < 105 colonies/ml urine of single uropathogen in patient being treated with appropriate antimicrobial therapy
- Physician's diagnosis
- Physician institutes appropriate antimicrobial therapy

xxii. Acute renal failure: In a patient who did not require dialysis preoperatively, worsening of renal dysfunction postoperatively requiring hemodialysis, ultrafiltration, or peritoneal dialysis. If the patient refuses dialysis but is deemed to have required it by the care team, this complication is coded as present.

xxiii. Progressive renal insufficiency: The reduced capacity of the kidney to perform its function as evidenced by a rise in creatinine of >2 mg/dl from preoperative value, but with no requirement for dialysis.

xxiv. Wound disruption or dehiscence: Separation of the layers of a surgical wound, which may be partial or complete, with disruption of the fascia.

xxv. Superficial surgical site infection: Infection that occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision and at least one of the following:

- Purulent drainage, with or without laboratory confirmation, from the superficial incision.

- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.

- At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by the surgeon, unless incision is culture-negative.

- Diagnosis of superficial incisional SSI by the surgeon or attending physician. Do not count the following conditions as SSI:

- Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).

- Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

xxvi. Organ space surgical site infection: An infection that occurs within

30 days after the operation and the infection appears to be related to the operation and the infection involves any part of the anatomy (e.g. organs or spaces), other than the incision, which was opened or manipulated during and operation and at least one of the following:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space
- Organisms isolated from an asecptically obtained culture of fluid or tissue in the organ/space
- An abcess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
- Diagnosis of an organ/space SSI by a surgeon or attending physician

xxvii. Deep wound surgical site infection: infection that occurs within 30 days after the operation and the infection appears to be related to the operation and infection involved deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following:

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
- A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (> 38 C), localized pain, or tenderness, unless site is culture-negative.
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
- Diagnosis of a deep incision SSI by a surgeon or attending physician.

-Note:

- Infection that involves both superficial and deep incision sites will be categorized as deep incisional SSI.
- An organ/space SSI that drains through the incision will be categorized as a deep incisional SSI.

b. Timing: Postoperative complications will be assessed prior to discharge and at the 2 week postoperative visit. Complications will be coded as present if identified at any time between the surgery and the 2 week visit.

6) Outcome: Operative and anesthesia times
   a. Measurement: Operative time will be recorded as the difference, in minutes, between the time of skin/wound closure and the time of surgical incision. Anesthesia time will be recorded as the difference, in minutes, between the time patients exit the operating room and the time of entrance to the operating room.
   b. Timing: Anesthesia intraoperative records routinely capture all four time points necessary to calculate the above outcomes. Records are scanned into the electronic medical record on the day of surgery and this data will be entered into the research record by research assistants on the day of surgery

(once the operation is complete).

7) Outcome: Recovery time (time spent in the post-anesthesia care and stepdown units)
    a. Measurement: Immediately following surgery, patients are typically transported directly to the post-anesthesia recovery unit for close monitoring by nursing staff and anesthesia faculty. Once the effects of anesthesia have diminished and patients are able to stay awake and maintain oxygenation without additional stimuli, they are transported to the stepdown unit for a period of observation to ensure they are able to ambulate and tolerate oral intake without nausea or vomiting. Time in the post-anesthesia care unit will be recorded as the difference between time of transport to the stepdown unit and the time of exit from the operating room. Time in the stepdown unit will be calculated as the difference between the time patients are discharged from the hospital (typically on the same day as surgery) and the time of transport from the post-anesthesia care unit. If patients are admitted rather than being discharged home on the same day as surgery, then stepdown time will be calculated as the difference between arrival in the inpatient or observation unit and the time of entrance to the stepdown unit. All values will be calculated in minutes.
    b. Timing: These values will be calculated on the day of surgery by research assistants.

Table 3. Analysis of secondary (clinical outcomes)		
Outcome	**Measurement**	**Number of items & time to completion**
Quality of life	Carolinas Comfort Scale	8 items Time to completion: 1 minute
Physical function	Katz index	6 items Time to completion: 2 minutes
Cognitive function	1) Confusion Assessment Method (short form) 2) Montreal Cognitive Assessment 5-minute form 3) Trail Making Test Parts A and B	1) 4 items, time to completion 5 minutes 2) 8 items, time to completion 5 minutes 3) 2 trails, time to completion 2 minutes
Pain	Visual Analog Scale	1 item Time to completion: 10 seconds
Postoperative complications	VA Surgical Quality Improvement Program definitions	Complications outlined above Assessed by research assistants and not participants
Operative and anesthesia times	Time from anesthesia note	Assessed by research assistants and not participants

Recovery time in post-anesthesia care unit and stepdown unit	Timer by research assistant	Assessed by research assistants and not participants

State and define the secondary outcome measures.

9.5 Data Analyses

9.5.1 Analysis of pilot/feasibility outcomes

We will use simple descriptive statistics (counts, ratios, mean/standard deviation, median/interquartile range, dispersion, proportions) to analyze the following outcomes: rate of enrollment and percent of eligible participants enrolled, reasons for non-enrollment, proportion of participants completing all visits, proportion of missing data, time to complete study evaluation and instruments, participant satisfaction.

To determine whether any study instruments are redundant and can be eliminated, we will run a series of linear regressions with one instrument score as the dependent variable and the other instruments and demographic variables as independent variables. This would take the form of the following, for example, where the Confusion Assessment Method (CAM) is the dependent variable for the first regression then becomes an independent variable for the second regression (and the FRAIL score becomes the dependent variable):

$$Regression\ 1: CAM = \propto + \beta_1 demographics\ (age, comorbidity, gender, race, etc) + \beta_2\ FRAIL + \beta_3 Katz + \beta_4 MoCA + \beta_5 Trail\ Making + \beta_6 CERAD + \beta_7 Pain + \beta_8 Carolinas\ Comfort\ Scale$$

$$Regression\ 2: FRAIL = \propto + \beta_1 demographics + \beta_2\ CAM + \beta_3 Katz + \beta_4 MoCA + \beta_5 Trail\ Making + \beta_6 CERAD + \beta_7 Pain + \beta_8 Carolinas\ Comfort\ Scale$$

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Additional regressions until all instruments have been tested

This process is repeated until all survey instruments have served as a dependent variable. We will calculate the adjusted R-squared for each regression, and this exceeds 40% (40% of the variance for that instrument is explained by the combination of participant demographics and other instruments), then that instrument is considered redundant and will be eliminated for future participants.[22] Standard regression diagnostics will be used and we will consider fractional polynomial modeling of all continuous variables as previously described.[31]

9.5.2 Analysis of secondary/clinical outcomes

For comparison of secondary/clinical outcomes we will use the Wilcoxon rank-sum test to compare continuous variables and the likelihood ratio chi-square to compare proportions of categorical variables. Our prior work suggests that there are no significant differences in effects by subgroups categorized by comorbidity or gender. Consequently, we do not plan any subgroup analysis.

Describe the descriptive and inferential statistical methods that will be used to analyze the outcomes and other study data. Specify any confounding variables for which it is anticipated adjustment will be made.

In accordance with NIH policy, unless data from prior studies strongly support no significant differences of clinical or public health importance in the intervention effect between gender and racial/ethnic subgroups, investigators should include a statement noting that a valid analysis of the intervention effect will be performed in these subgroups. If data from prior studies do not strongly support the existence of significant differences in the intervention effect between subgroups, then the analyses need not have high statistical power for detecting clinically meaningful differences.

9.5.3 Missing data

A complete-case analysis will be performed for the primary analysis of survey and other data. To test sensitivity of the survey results to missing data, we will use multiple imputation with either Poisson or negative binomial regression (depending on overdispersion). For instruments scored by time to completion, we will employ multiple imputation with chained equations. Analysis will then proceed using post-imputation methods that take into account the variance of imputed values across samples (i.e. "pooling rules").

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data will be collected for each participant by a research assistant blinded to the treatment assignment. For the baseline assessment, all forms will be completed after verifying eligibility but before opening the envelope with the treatment assignment. For subsequent assessments, another research assistant not familiar with the patient's assignment will complete all case report forms. Every case report form will be reviewed, approved, and signed by the site principal investigator and by the project principal investigator.

Case report forms will be provided for each patient and instructions for completion maintained in our Manual of Procedures, which will be given to study staff at each participating site.

Data will be entered into an online, secure REDCap database to help maintain participant confidentiality. Additionally, separate databases will be maintained with (1) participant identifying information and (2) data from case report forms, which will be labeled with the participant's study number. After entering data into the database, the participant can only be

identified by combining the two datasets. Otherwise, all data entry is guided by the participant's study identification number.

Indicate how information will be collected for each participant and by whom. For example if a blinded observer will perform outcome assessments, state who this person will be. Describe methods for maintaining confidentiality of participant records. Refer to Manual of Procedures (MOP) for description of study forms (also called Case Report Forms).

10.2 Data Management

The principal investigator will monitor data for both sites. The principal investigator will design and modify the study data and the REDCap database storing research data. The principal investigator will also be responsible for performing quality control checks, preparing data quality reports, and preparing progress reports. In consult with the biostatistician (Dr. Reisch), the principal investigator will be responsible for design and analysis of research questions.

The site principal investigator in Houston will assist with data monitoring at that site.

There will not be a data coordinating or management center.

Data collection forms will be maintained in paper and electronic forms.

The principal investigator will maintain records in accordance with good clinical practice guidelines that include:

1. IRB correspondence related to the clinical protocol, including but not limited to approval notifications, adverse event reports, and interim reports.
2. Current and past versions of IRB-approved protocols, consent forms, and subject recruitment pamphlets
3. Signed investigator agreements and certification of financial conflicts of interest
4. Bio sketches for all study staff
5. Certificates of required research training for all study staff
6. Master randomization list
7. Signed consent forms
8. Complete Case Report Forms signed and dated by the investigator
9. Source documents or certified copies of source documents
10. Copies of correspondence to site investigator
11. Subject screening and enrollment logs
12. Subject identification code list
13. Final clinical study report

The investigator will retain the above records and reports for up to two years after the study is complete.

Briefly describe clinical site responsibilities in data collection and management.

Briefly describe Coordinating Center (or Data Management/Statistical Center) responsibilities in data management.

Briefly describe data collection forms.

10.3 Quality Assurance

10.3.1 Training

10.3.1.1 Surgeon training in use of local anesthesia

All participating surgeons will undergo training in the injection of local anesthesia for inguinal hernia repair. The training will consist of either in person or video training with the principal investigator serving as instructor. Instruction will consist of two parts: a slideshow demonstrating pictures of the technique and practice performing the injection. For the practice session, a chicken breast purchased from a local grocery store will serve as the practice site for injection. Under supervision of the principal investigator, the participant and surgeon will first mark a practice "incision" on the chicken and inject the "skin" with 10 mL of the local anesthesia mix, using a 10cc syringe. The surgeon will then hub the syringe to practice injecting the deep tissue and fascia along the length of the incision. To verify application of the above training and practice, the principal investigator will observe (either in person or by video) the first operation under local anesthesia by each surgeon.

A brief training session will be repeated after the first six months to reinforce study protocols.

10.3.1.2 Training of research assistants

All research assistants at both sites will undergo in person or video training for all study protocols. The training will include thoroughly reviewing the study manual of procedures. Training will also include administration of all study instruments to mock participants, with feedback from the principal investigator on performance.

Training of research assistants will be repeated every six months to reinforce study protocols. If new research assistants are hired as the study progresses, they will undergo training prior to first approaching patients.

Describe types and mechanisms of training of staff for the study.

10.3.2 Quality Control Committee

There will not be a quality control committee. The principal investigator will be responsible for quality control.

10.3.3 Metrics

Metrics for quality control include the following:

- Successful completion of all training activities for surgeons and research assistants

- Successful administration of study instruments to mock participants
- Number of deviations from protocol
- Number of data entry errors
- Proportion of eligible patients approached for enrollment

Provide quality control metrics for outcome measures.

10.3.4 Protocol Deviations

The research team must not make any changes to or deviate from the protocol, except to protect the life and well-being of participants in emergencies. Whenever a deviation occurs, the investigator and IRB will be notified as soon as possible, and no later than 5 working days after the deviation. The reason for the deviation and date of occurrence will be documented and reported to the investigator and the IRB using the appropriate case report form. Deviations will be reviewed and evaluated at each bi-weekly team meeting following a report, and appropriate corrective and preventive actions will be initiated.

Reasons for deviations will be classified as follows:

- Type A: to protect the life or physical well-being of the subject in an unforeseen emergency
- Type B: medical judgment
- Type C: misunderstanding of protocol requirements
- Type D: situation beyond the control of the study team
- Type E: oversight, error, or protocol noncompliance

If there is a trend or pattern observed for a particular deviation type, the investigator will conduct a compliance visit and to document any corrective steps or training in the study regulatory binder.

Describe how protocol deviations will be captured, documented, and reviewed.

10.3.5 Monitoring

As mentioned above, the team will have video meetings every two weeks to review progress and monitor quality. Additionally, UT Southwestern will provide a qualified monitor to ensure compliance with protocols and agreements. Routine monitoring will occur to:

- Verify subject enrollment is achieved
- Verify inclusion and exclusion criteria are appropriately applied at enrollment
- Verify the correct version of informed consent documents are used
- Review medical records of all enrolled subjects to ensure adverse events have been captured and properly reported
- Verify data are complete and backed up by source documents
- Verify all contracts, certifications, and medical licenses for each site are valid and maintained throughout the study

Briefly describe methods (e.g., site monitoring) for assuring protocol compliance, and data quality at the clinical sites, including review of records, consent forms, etc. The

types of materials to be reviewed; who is responsible, and the schedule for reviews may be specified or referenced in the Manual of Procedures (MOP).

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

The texts in this section are examples only.

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (Appendix) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g. person with power of attorney), this individual must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record.

11.3 Participant Confidentiality

Any data, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB will review all study documentation to safeguard participants' rights, safety, and well-being. The protocol, study pamphlets, a sample informed consent, written information for the subjects, safety updates, progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

Include in this section the guiding ethical principles being followed by the study. If the study is conducted at international sites, consider including reference to the Declaration of Helsinki,

CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), or another country's ethical policy statement, whichever provides the most protection to human subjects.

13 COMMITTEES

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the principal investigator, all coinvestigators, principal investigators for each site, and collaborators. That Steering Committee will meet in person or by video every six months.

Provide a list of the committees (Steering Committee or Executive Committee, Publication Committee, Adjudication Committee, etc.) and describe their roles.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NIA prior to submission.

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16 SUPPLEMENTS/APPENDICES

17

PROTOCOL NUMBER: #19-108

PRINCIPAL INVESTIGATOR: Courtney J. Balentine, MD
4500 S. Lancaster Drive
Dallas, TX 75216

STUDY-RELATED PHONE NUMBERS: (214)857-1618
(214)857-1622

SUMMARY

Before agreeing to take part in this research study, it is important that you **read and understand** the procedures, benefits, risks, and discomforts associated with the study. It describes other treatments that are available to you in addition to explaining your right to withdraw from the study. It is important for you to understand that no promises can be made about the results of the study. If you decide to take part in this study, you must sign this form to show that you want to participate. You will be given a copy of this informed consent for your records.

A. WHAT IS THE STUDY ABOUT AND WHY ARE WE DOING IT?

We are asking you to choose whether or not to volunteer for a research study. This study is designed to help us understand more about groin hernia repairs. We are trying to determine the ideal medication to decrease pain for groin hernia surgery in older adults. We want to know how patients feel after surgery using a drug which puts you to sleep or a drug which makes the area numb. We will assess how quickly you return to normal. We have included detailed information. Ask the research team questions. Taking part in this study is completely up to you.

B. WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

By doing this study, we hope to learn more about inguinal hernia repairs. Your participation in this study will last about six months. The study will last two years.

C. WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You will help us determine the ideal medication to eliminate the feeling of pain during groin hernia surgery. For a complete description of benefits, refer to the Detailed Consent.

D. WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

If you agree to take part, you will be assigned to receive a medication to eliminate pain by putting you to sleep or by numbing the area. Some people would prefer to choose which type of drug to eliminate pain during surgery.

This study requires more interviews and contact than normal hernia surgery.

For a complete description of risks and alternatives refer to the Detailed Consent.

E. DO YOU HAVE TO TAKE PART IN THE STUDY?

You do not have to take part in this study. If you choose not to take part, it will not in any way affect your care. If you decide to take part in the study, it should be because you really want to volunteer.

F. WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

The person in charge of the study is Dr. Courtney Balentine of the VANTHCS. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study his contact information is (214)857-1618.

DETAILED CONSENT

1. WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to learn more about groin hernia repairs. We want to determine if a drug to eliminate pain by numbing the area is better for older adults than a medication which puts you to sleep. We expect to learn if how fast you recover depends on which medication we give you.

2. HOW LONG WILL I BE IN THE STUDY?

The study lasts two years in total. Your participation in the study will last up to 6 months.

3. WHAT WILL HAPPEN IF I TAKE PART IN THE STUDY?

If you agree to participate, you will be chosen to receive a drug to eliminate the feeling of pain by putting you to sleep or by making the area numb. We plan to include up to 60 patients in the study, with 30 in each group. The study is broken up into six parts which are noted below:

1. Before surgery clinic visit: After you have agreed to participate in the study, we will administer surveys which you will complete. This portion of the clinic

visit will last about 30 minutes. We will assess how well you are able to complete basic skills. We will test your memory, focus, attention, frailty, and pain. We will ask about your hernia-related quality of life. At this visit we will not ask you to have any blood drawn. The only blood tests for you will be the ones ordered by your surgeon that are standard before surgery.

2. Surgery: During surgery, we will record your heart rate, blood pressure, and oxygen level. We will record how long the surgery takes.

3. Recovery unit: Following surgery you will likely be allowed to go home. We will keep you in the recovery room until you are able to manage basic self-care. We will monitor your heart rate, blood pressure, and oxygen saturation.

   You will complete the same surveys that you did in clinic which will take about 30 minutes and be administered prior to discharge from the recovery unit. We will record the amount of time you spent in the recovery unit. We will make sure that you are able to use the bathroom. We will monitor if you require admission to the hospital and record complications.

4. 2-5 days after the surgery: You will receive a phone call two days after surgery. This phone call will last up to 30 minutes. We will administer surveys over the phone. These will assess how well you are able to perform basic skills, your attention, memory, risk of delirium, and pain level. We will also discuss your hernia-related quality of life. We will discuss any complications that may have occurred.

5. Clinic visit after surgery: You will come to clinic two weeks after surgery. You will see your doctor and have your wound checked. We will obtain vital signs and discuss complications. We will administer surveys to assess basic skills, your thinking, and pain. Once again, we will discuss hernia-related quality of

life. This portion will take about 30 minutes.

6. 6 months after surgery phone call: The final time point will be 6 months after your surgery. This will last up to 30 minutes. We will call you to evaluate your ability to perform basic skills and how well you are thinking. We will ask about your pain related to your hernia surgery, and any complications. We will discuss your hernia-related quality of life.

4. WHAT IS EXPECTED IF I TAKE PART IN THIS STUDY?

If you decide to take part in the study, you will be expected to take part in the time points listed above. You will not be able to choose if you receive a drug to eliminate pain by putting you to sleep or by numbing the area. The type of medication you get will be assigned by chance.

If you are selected to receive the numbing medicine, it will be provided by your surgeon. We will numb all layers of your skin and tissue until you are unable to feel the area. If at any time during the surgery, you become uncomfortable let your doctors know and we will provide more numbing medicine. If you are unable to lie still or be comfortable during the procedure you may require stronger medicine to put you to sleep. This will be based on the surgeons and anesthesiologists discretion. If they feel that it is unsafe to continue with numbing medication alone, they may give you medication to put you all the way to sleep.

If you are selected to receive the medication which puts you all the way to sleep, this will be done by the anesthesiologist. You will have a breathing tube in place to keep you safely breathing throughout the procedure.

You will have your hernia repaired as planned at the North Texas VA Health Care System. You will have normal clinic visits at the general surgery clinic before and

after surgery. You will receive two additional phone calls after your surgery.

You will be expected to keep your appointments, which is the visit before surgery and two weeks after surgery. If you miss your appointment, please contact the general surgery clinic to reschedule. You will also be expected to participate in the telephone calls after surgery.

While participating in this research study do not take part in any other research project without approval from the investigators.

Ask questions when you think of them.

5. WHAT ARE MY RISKS?

For all surgeries there are risks, and this surgery is no different. The main risks of the study are the same as a normal inguinal hernia repair and your surgeon will discuss the risks of inguinal hernia surgery with you separately.

Risk of the drug used to eliminate the feeling of pain by putting you to sleep:

- "Malignant hyperthermia" is a rare side effect of the medication which puts you to sleep during surgery. Patients may develop high temperature, blood pressure changes, and kidney failure. This is life threatening if it occurs. If you or your family member has had a reaction to any medications for surgery in the past you should mention this to your doctor. This occurs in less than 0.001% of patients.
- Urinary retention is a more common side effect of general anesthesia which means that you may have difficulty urinating. Most of the time this gets better over time, but you may require a catheter in your bladder to help with urination. This can occur in up to 5% of patients.
- This medication can have changes to your memory or your ability to care for yourself. It is not known exactly how common this is, but the risk increases with age. This typically will resolve without intervention but may require admission to the hospital to ensure you are able to care for yourself before you are discharged.

- You may experience changes to your blood pressure or heart rate during the surgery. These changes occur in up to 10% of patients. If these are severe and we feel that it is unsafe to discharge you home, you may require admission to the hospital to ensure it is safe for you to go home.
- Postoperative nausea and vomiting may also occur after receiving this medication. This occurs in up to 10% of patients. We will give you a medicine before surgery to prevent this complication.
- You may also have complications related the to breathing tube in place during surgery. Most of the time this is limited to a sore throat (up to 10%) which goes away on its own but also may progress to pneumonia (<2%) which could require admission to the hospital for antibiotics. There may also be complications related to your teeth following insertion of the tube such as tooth chipping or a cut to your lips (<0.02%).

Risk of the drug to decrease the feeling of pain by numbing the area of the surgery:

- You may develop an allergic reaction to the medication. If this occurs, you will be given a medication to alleviate the discomfort/reaction which typically involves itching near the incision. In very rare occasions (<0.01%) patients have severe allergic reactions which may require further hospitalization.
- You may also experience pain or discomfort during administration of the numbing medication. This typically only lasts for a couple of seconds and then goes away. If you have any discomfort during the surgery let your doctors know and you will be given more numbing medicine.

There is always a chance that any procedure can harm you. The procedures in this study are no different. In addition to the risks described above, you may experience a previously unknown risk or side effect.

Risks of the usual care you receive are not risks of this study. Not all of these risks are included in this consent form. You should talk with your health care providers if you have any questions about the risks of usual care.

Additionally, you may experience feelings of being uncomfortable when answering the survey questions. If this occurs, we can refer to you to the psychology department and you do not have to complete the survey.

6. WHAT ARE POSSIBLE BENEFITS OF THIS STUDY?

You may have a faster recovery if you receive numbing medication. The primary benefit of the study will be to help future patients undergoing hernia surgery.

7. WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO JOIN THIS STUDY?

You may choose to not participate in this research study. If you choose not to participate your surgery will still be performed as planned.

8. HOW WILL MY PRIVATE INFORMATION BE PROTECTED?

We will keep your research records private. No one has access to any paperwork about your participation except as required by law. All of your records will be kept within the password protected VA network and in a locked office.

Identifiers might be removed from the identifiable private information or identifiable biospecimens that are collected. After that removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from you or your legally authorized representative.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time once the trial is registered.

9. WHAT ARE THE COSTS TO ME IF I TAKE PART IN THIS STUDY?

You will not be charged for any treatments or procedures that are part of this study. If you usually pay co-payments for VA care and medications, you will still pay these co-payments for VA care and medications that are not part of this study.

There is no cost to you for participating in this study. The study does take a lot of time in addition to your normal operation and after surgery clinic visit. You will receive a $20 gift card for each point associated with the study. These visits include the preoperative visit, the 48-hour postoperative phone call, the 2-week postoperative clinic visit, and the 6-month postoperative phone call. If you participate in each time point (4) you will receive $80 in gift cards. If you drop out before the end of the study, you will receive a gift card for each completed portion of the study.

10. WHAT WILL HAPPEN IF I AM INJURED BECAUSE OF MY BEING IN THE STUDY?

The VA is required to provide medical treatment to participants injured by participation in a VA study. If you are injured as a result of being in this study, the VA will provide the necessary medical treatment in accordance with federal law. There are no plans to provide any other payments or other forms of compensation for a study-related injury (for example, for lost wages or discomfort). You do not give up any legal rights by signing this consent form.

You may contact the research team at the following numbers:

DURING THE DAY:

Dr. Courtney Balentine at *(214)857-1618*

AFTER HOURS:

Dr. Courtney Balentine at *1(800)725-4436*

Emergency and ongoing medical treatment will be provided as needed.

The DVARC answering service is available at 800-725-4436 to receive calls from patients after hours.

Emergency and ongoing medical treatment will be provided as needed.

11. DO I HAVE TO TAKE PART IN THE STUDY?

Taking part in this study is voluntary and you may refuse to take part without penalty or loss of benefits to which you are otherwise entitled. You are free to withdraw your consent and stop taking part at any time. Not taking part in the study will in no way affect the quality of care you receive now or in the future from the VA. This will also not affect your right to take part in other studies. The study doctors will answer any questions you may have about the study. If you decide to withdraw, the information already collected may be used for remainder of the study.

You must let the study doctor know if you do decide to withdraw from the study.

12. WHO DO I CONTACT ABOUT THIS STUDY IF I HAVE QUESTIONS?

If you have any questions about this study or have any bad effects of your treatment, you should call the study doctor, Dr. Courtney Balentine, at 214-857-1618, or a member of the research team at 214-857-1622.

If you have a medical emergency, you should immediately call 911 for assistance. If you have questions about your rights as a study participant, or you want to make sure

this is a valid VA study, you may contact the Institutional Review Board (IRB). This is the Board that is responsible for overseeing the safety of human participants in this study. You may call the Research Compliance Officer (RCO) at (214) 857-0341 if you have questions, complaints or concerns about the study or if you would like to obtain information or offer input.

If you have any questions about your rights as a research subject, complaints about your treatment or general concerns about the conduct of the research study, of if you have questions, complains, concerns you may contact the Dallas VAMC Patient Representatives at 214-857-0482. The Patient Representative will guide you in resolving your question or complaint.

If you have a medical emergency, you should immediately call 911 for assistance.

14. WILL I BE TOLD NEW INFORMATION ABOUT THIS STUDY?

Any significant new findings that develop during the course of the research study that the study doctor thinks may affect your willingness to continue to take part will be given to you as soon as possible. Clinically relevant research results will not be disclosed to subjects.

15. WHO COULD PROFIT FROM THE STUDY RESULTS?

There will be no payments made to investigators which could be construed as a potential conflict of interest. There will be no specimens collected which could be used for commercial profit.

16. DOES THIS STUDY INVOLVE GENETIC RESEARCH? HOW WILL MY GENETIC INFORMATION BE PROTECTED?

This study does not involve genetic research.

17. FUTURE USE OF DATA AND RE-CONTACT

The data will not be retained after the study for future use.

18. DOES THIS STUDY INVOLVE TISSUE BANKING?

This study does not involve tissue banking.

19. AGREEMENT TO PARTICIPATE IN THE RESEARCH STUDY

_____ _____has explained the research study to you. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You have been given the chance to ask questions and obtain answers.

By signing this document below, you voluntarily consent to participate in this study. You also confirm that you have read this consent, or it has been read to you. You will receive a copy of this consent after you sign it.

I agree to participate in this research study as has been explained in this document.		
_____ Participant's Name	_____ Participant's Signature	_____ Date
_____ Legally Authorized Representative Name	_____ Legally Authorized Representative Signature	_____ Date